

Rapid-Acting Insulins
 Insulin Aspart (NovoLog®—Novo Nordisk)
 Insulin Glulisine (Apidra®—Sanofi Aventis)
 Insulin Lispro (Humalog®—Eli Lilly)
 Regular Human Insulin (Humulin® R—Lilly; Novolin® R—Novo Nordisk)
 AHFS 68:20.08, Insulins

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Executive Summary

Introduction: Insulin is a cornerstone of diabetes treatment, replacing or supplementing endogenous pancreatic insulin. Rapid-acting insulins (ie, regular, aspart, glulisine, and lispro) have a rapid onset and short duration of action. These agents are generally used to control meal-related hyperglycemia or for continuous subcutaneous insulin infusion pumps (CSII or insulin pump). Rapid-acting insulin analogs (ie, aspart, glulisine, and lispro) have a more rapid onset and shorter duration than regular insulin, but produce similar results. American Diabetes Association guidelines do not specify a preference between these insulins.

Efficacy: Insulins aspart and lispro have all been compared to regular insulin in a variety of patient populations (eg. type 1 and type 2 diabetes, pregnancy, pediatrics). No trials compare glulisine to other rapid-acting insulins in pregnant patients or pediatric patients. Head-to-head comparisons between insulins aspart, glulisine, and lispro are not available in all patient populations.

- How does glycemic control in type 1 diabetes compare between the different rapid-acting insulins?

Twenty-two studies were included comparing rapid-acting insulins. Insulin aspart was at least as effective as regular insulin in six trials. Glulisine was equally effective to lispro in one trial and was at least as effective to regular insulin in one trial. Lispro was at least as effective to regular insulin in 14 trials. Aspart insulin decreased A1C by 0.06% to 0.34% from baseline in 5 trials and increased A1C 0.01% in one trial. Glulisine decreased A1C by 0.14% to 0.46% before meals and by 0.11% after meals. Lispro insulin decreased A1C by 0.1% to 6% in 10 trials and increased A1C 0.1% to 0.3% in 2 trials from baseline. Among all trials, regular insulin increased A1C by 0.02% to 0.4% in 4 trials and decreased A1C by 0.02% to 5% in 14 trials.

- How does glycemic control in type 2 diabetes compare between the different rapid-acting insulins?

Nine trials compared a rapid-acting insulin analog and regular insulin in patients with type 2 diabetes. One trial found a significantly greater change in A1C with insulin aspart compared to regular insulin. Glulisine was at least as effective as regular insulin in two trials. Insulin lispro was also at least as effective as regular insulin in six trials. Aspart insulin improved A1C by 0.4% in one trial. Glulisine improved A1C by 0.32% to 0.46% in one trial. Lispro improved A1C by 0.5% to 3.2% in 5 trials. In 7 trials, regular insulin improved A1C by 0.3% to 2.7%.

- How does glycemic control in gestational diabetes compare between the different rapid-acting insulins?

No trials evaluate glulisine in gestational diabetes. Three trials compared the use of lispro or aspart to regular insulin in patients with gestational diabetes. Insulin aspart and insulin lispro were at least as effective as regular insulin.

- How does glycemic control compare between the different rapid-acting insulins in pregnant patients, other than those with gestational diabetes?

No trials evaluated the use of insulin glulisine in patients with pregestational diabetes. Two trials compared the use of lispro or aspart to regular insulin in pregnant, type 1 diabetic patients. Insulin aspart and insulin lispro were both at least as effective as regular insulin in pregnant patients.

- How does glycemic control compare between the different rapid-acting insulins when treating pediatric patients?

There are no trials comparing insulin glulisine to other rapid-acting agents in pediatric patients. Seven trials compared a rapid-acting insulin analog and regular insulin in pediatric patients. Insulin aspart was equally effective to insulin lispro in one study. Insulin aspart was at least as effective as regular insulin in a single trial of 30 patients. Insulin lispro was equally effective to regular insulin in four trials. The range of change in A1C following lispro in these trials ranged from 0% to +0.5%. In contrast, A1C change with regular insulin ranged from no change to a decrease of 0.4%.

- How does glycemic control compare between the different rapid-acting insulins when they are administered via continuous subcutaneous insulin infusion (CSII or insulin pumps)?

Seven trials in patients with type 1 diabetes compared insulin aspart, insulin lispro, or insulin glulisine to regular insulin via continuous subcutaneous infusion. Insulin glulisine was as effective as insulin aspart in two studies. Insulin aspart was equally effective to regular insulin in one study. Insulin lispro was equally effective to regular insulin in one study but in 5 other studies was shown to be more effective than regular insulin in terms of A1C reductions compared to baseline.

Adverse Effects:

- How does the safety of the rapid-acting insulins compare with each other?

The adverse events are similar among insulin products, except for hypoglycemia. Hypoglycemia may be more common with regular insulin than rapid-acting insulin analogs, as described below.

- How do the rapid-acting insulins compare in terms of hypoglycemia?

Of the 29 trials that evaluated hypoglycemia in patients using multiple daily injections, 9 found significant differences in favor of the rapid-acting insulin over regular insulin. The other 20 trials found no difference. Hypoglycemia may be more common with regular insulin than insulins aspart, glulisine, and lispro. Two of the 7 trials comparing aspart and regular insulin found more hypoglycemia in the regular insulin groups compared to aspart insulin groups. No trials comparing glulisine to regular insulin or lispro found a significant difference for hypoglycemic events between the groups. Seven of the 18 trials that evaluated lispro and regular insulin reported significantly more hypoglycemia in the regular insulin groups.

Of the 15 multiple daily injection trials that evaluated nocturnal hypoglycemia, 7 found significant differences favoring the rapid-acting insulin over regular insulin. Two of five trials that evaluated nocturnal hypoglycemia with aspart and regular insulin found more events in the regular insulin group. Only 1 of the 4 trials comparing glulisine to regular insulin or lispro found an increase with nocturnal hypoglycemia events with regular insulins. Of the 6 trials evaluating nocturnal hypoglycemia in patients treated with regular or lispro, 4 found significantly more events with regular insulin.

Of 7 continuous subcutaneous infusion studies evaluating hypoglycemia, one trial reported significantly less hypoglycemic episodes per patient month with insulin aspart (6.7 ± 5.4) than with lispro (10.5 ± 8.1 ; $p < 0.05$) or regular insulin (10.5 ± 8.9 ; $p < 0.05$). The remaining 5 trials comparing lispro to regular insulin found no significant difference in the incidence of hypoglycemia.

- How does the safety of the rapid-acting insulins compare with each other in special populations?

Of the three trials that compared lispro and regular insulin in patients with gestational diabetes, none found significant differences in maternal or neonatal adverse events. Hypoglycemia was not assessed in these three trials.

Two trials reported hypoglycemia outcomes in pregnant, type 1 diabetic patients receiving either lispro, aspart or regular insulin. One trial found no difference in the number of patients who experienced hypoglycemia symptoms, but found a greater proportion of patients in the lispro insulin group experienced blood glucose < 54 mg/dL compared to the regular insulin group (5.5% vs. 3.9%, $p < 0.05$). Three other trials found no difference in maternal or neonatal complications when comparing lispro to regular insulin.

Seven trials reported adverse event outcomes in comparative trials between lispro and regular insulin. No difference in hypoglycemia was observed in a study comparing aspart to either lispro or regular insulin. Hypoglycemia may be less in pediatric patients treated with lispro compared to regular insulin; lower hypoglycemia with lispro was reported in one of five regular insulin comparator studies.

Summary: The rapid-acting insulins are effective for type 1 and type 2 diabetes, as well as in pediatrics, pregnant patients, and patients with gestational diabetes. Several trials compared the rapid-acting insulin analogs with regular insulin. There were no consistent significant differences in efficacy results (ie. A1C) between the rapid-acting insulin analogs. Reductions in A1C with lispro, glulisine, and aspart were equal to or greater than A1C reductions seen with regular insulin. All of the rapid-acting insulins possess a similar adverse event profile with hypoglycemia being the most common and most serious adverse event. Rates of hypoglycemia were occasionally lower with lispro, aspart, or glulisine compared to regular insulin; however, this was not consistently seen across all trials.

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Introduction

Insulin is a cornerstone of diabetes treatment.¹ Insulins are generally categorized according to their onset and duration of action: rapid/short-acting, long-acting, and biphasic insulin mixtures.^{2,3} This review focuses on rapid-acting insulins. The term “rapid-acting” often applies only to insulin analogs with a more rapid onset of action than regular human insulin (ie, aspart, glulisine, lispro). In this monograph, regular insulin is also considered a rapid-acting insulin. This monograph includes all FDA approved monophasic insulins commonly injected subcutaneously to control meal-related hyperglycemia or administered via continuous subcutaneous insulin infusion (CSII, insulin pump). The specific products addressed in this monograph include regular human insulin (Humulin® R, Novolin® R), insulin aspart (Novolog®), insulin glulisine (Apidra®), and insulin lispro (Humalog®).⁴⁻⁹ Commercially available regular human insulins are produced using recombinant DNA technology. The resulting product is structurally identical to endogenous human insulin.^{4,5} Aspart, glulisine, and lispro are human insulin analogs, also produced using recombinant DNA technology. Slight alterations in the amino acid sequences of these analogs results in a more rapid onset and shorter duration of action compared to regular insulin, while maintaining the same hypoglycemic potency.⁷⁻⁹ The available rapid-acting insulins are compared in Table 1.

Table 1. Comparison of the Rapid-Acting Insulins²⁻¹⁰

Characteristic	Human Regular (Humulin, Novolin)	Aspart (Novolog)	Glulisine (Apidra)	Lispro (Humalog)
Time Action Profile				
Onset	30 – 60 minutes	10 – 30 minutes	10 – 30 minutes	10 – 30 minutes
Peak Effect	2 – 5 hours	1 – 3 hours	1 – 3 hours	30 – 90 minutes
Duration	3 – 10 hours	3 – 5 hours	3 – 4 hours	3 – 4 hours
Other Characteristics				
Available Forms ^a	10 mL vials Humulin 20 mL vials 500 units/mL Novolin 5 x 3 mL Penfill® cartridges for use in PenFill® insulin delivery device	10 mL vials 5 x 3 mL Penfill® cartridges for use in PenFill® delivery device 5 x 3 mL FlexPen® prefilled pen	10 mL vials 5 x 3 mL cartridges for use in OptiClick® delivery device	10 mL vials 5 x 3 mL cartridge system ^b 5 x 3 mL KwikPen™ prefilled pen
Compatible with subcutaneous insulin pump	Yes	Yes	Yes	Yes

Characteristic	Human Regular (Humulin, Novolin)	Aspart (Novolog)	Glulisine (Apidra)	Lispro (Humalog)
Compatible for mixing with other insulins ^c	NPH	NPH	NPH	NPH

^aAll product concentrations are 100 units/mL unless stated.

^bFor use with multiple reusable pen and pump systems from a variety of manufacturers including Lilly.

^cWhen used in a subcutaneous pump, insulins must not be mixed.

Pharmacology

Insulin preparations are administered to replace endogenous insulin in patients with insufficient insulin production associated with diabetes mellitus. Insulin is a polypeptide that regulates metabolism and storage of carbohydrates, fats, and proteins. Exogenous insulin's effects in diabetes are primarily measured in terms of blood glucose reduction, although exogenous insulin possesses all of the metabolic properties of endogenous insulin. The pharmacologic activity of insulin analogs (eg, aspart, glulisine, lispro) is identical to regular insulin. Only the onset and duration of action are altered.^{4, 6-9}

Disease Overview

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia. Type 1 diabetes is primarily characterized as a lack of insulin production. Type 2 diabetes generally begins as an inability to efficiently utilize endogenous insulin, with decreased insulin production as the disease progresses. The third major form is gestational diabetes, characterized by glucose intolerance during pregnancy.¹¹ The exact pathophysiology of gestational diabetes is not well defined, but it may be due to chronic, rather than acute, beta-cell defect. Pregnancy may simply unmask or worsen pre-existing glucose intolerance, rather than inducing glucose intolerance. The majority of women experiencing gestational diabetes will develop diabetes at some point after pregnancy.¹² Approximately 1-5% of diabetes cases do not match the standard classifications of type 1, type 2, or gestational diabetes.¹¹

A recent press release by the Centers for Disease Control and Prevention (CDC) reported that approximately 24 million people in the United States (US) have diabetes.¹³ This figure represents approximately 8% of the US population and an increase of approximately 3 million people over the past 2 years. The CDC estimates that 25% of patients with diabetes are not aware that they have the disease. Additionally, 57 million people have pre-diabetes, a major risk factor for developing diabetes.¹³ Estimated direct and indirect costs of diabetes were \$174 billion in 2007.¹¹

The primary diagnosis and treatment guidelines for diabetes types 1 and 2 are published by the American Diabetes Association (ADA, 2008).¹ Core guidelines for gestational diabetes include the ADA guidelines (2008), as well as the International Workshop-Conference on Gestational Diabetes Mellitus recommendations (2007).^{1, 12} Neither of these guidelines specify a preference between the different rapid-acting insulins examined in this monograph.^{1, 12}

Diabetes Types 1 and 2

The majority of complications caused by diabetes are categorized as either microvascular or macrovascular in origin. Microvascular complications include retinopathy, nephropathy, and neuropathy. Macrovascular complications include coronary heart disease, myocardial infarction, stroke, and peripheral vascular disease.¹ Intensive glycemic control is directly related to a reduction in microvascular complications. For every 1% drop in hemoglobin A_{1c} (A1C), the risk of microvascular complications decreases by 40%.¹ The effects of intensive glycemic control on macrovascular complications is unclear at this time. Some evidence suggests reduced macrovascular risk with near-normal glycemia, while other evidence does not support a risk reduction, and may even suggest increased cardiovascular risk when glycemic control is very intensive.¹³⁻¹⁷ The key glycemic measure recognized by the ADA is A1C. The ADA recognizes self-monitored blood glucose (eg, fasting, preprandial, or postprandial blood glucose) as important for achieving the desired A1C. Unlike A1C, blood glucose measurements have not been directly linked to decreases in diabetes complications. The A1C goal for adults is < 7%. A small additional benefit may be seen with select individuals using a target A1C of < 6%. Children, patients with a history of severe hypoglycemic events, those with limited life expectancies, and patients with certain comorbid conditions may benefit from less stringent A1C goals.¹ Target A1C levels in children and adolescents are displayed in Table 2.

Table 2. Glycemic Goals in Children and Adolescents¹

Age	Target A1C
0 – 6 years	7.6 – 8.4%
6 – 12 years	< 8%
18 – 19 years	< 7.5%

Gestational Diabetes

Gestational diabetes increases the risk of fetal and maternal complications during pregnancy.^{12, 18} Increased risks to the fetus or neonate include spontaneous miscarriage, macrosomia (excessive fetal growth), fetal malformations, cardiovascular or central nervous system abnormalities, hypoglycemia, hypocalcemia, hyperbilirubinemia, hypomagnesemia, and respiratory distress syndrome. The pregnant mother is at increased risk for pre-eclampsia, preterm labor, birth trauma or cesarean section, or postpartum complications. Risk of complications is related to pregestational blood glucose control and postprandial blood glucose control during pregnancy. Long-term data are lacking regarding the effect of glucose control on outcomes in gestational diabetes. Fetal death is decreased through glucose control, but the effects of glucose control measures on morbidity are unclear. Because of the relatively short treatment period of gestational diabetes, glycemic goals are in terms of blood glucose levels rather than A1C.^{1, 12} Table 3 lists the glycemic goals in patients with gestational diabetes.

Table 3. Glycemic Goals in Gestational Diabetes^{1, 12}

Time of Measurement	Target Blood Glucose Levels	
	American Diabetes Association (ADA)	5th International Conference on Gestational Diabetes
Preprandial	≤ 105 mg/dL	< 96 mg/dL
1 hour postprandial	≤ 155 mg/dL	< 140 mg/dL
2 hour postprandial	≤ 130 mg/dL	< 120 mg/dL

Treatments

Pharmacologic agents used for the treatment of diabetes include exogenous insulin and oral glycemic control agents. Insulin is the cornerstone of therapy for patients with type 1 diabetes. Patients with type 2 diabetes are generally managed with lifestyle modifications and oral agents as long as possible, but will usually require insulin therapy.¹⁰ Patients with gestational diabetes are treated with lifestyle modifications, advancing to insulin therapy if necessary to achieve blood glucose goals or if there is evidence of macrosomia. Oral diabetes medications are not generally recommended in gestational diabetes due to a lack of evidence in this clinical setting.¹² Patients with diabetes who become pregnant are treated with insulin because of insufficient evidence for oral antidiabetic agents in early pregnancy.¹⁹

The therapeutic goal of insulin therapy is to mimic normal pancreatic insulin release as closely as possible.¹ In non-diabetic patients, the pancreas secretes a constant basal level of insulin into the blood. Insulin boluses are also released from the pancreas in response to postprandial blood glucose elevations. A combination of long- and rapid-acting insulin products is commonly used in insulin dependent diabetic patients to mimic normal pancreatic function.¹⁰ For optimal blood glucose control, peak levels of exogenously administered rapid-acting insulin should coincide with peak postprandial blood glucose levels. When regular human insulin is administered immediately before a meal, peak serum insulin concentrations do not occur until after the postprandial blood glucose peak, resulting in elevated postprandial blood glucose levels. Administering regular human insulin 15 to 30 minutes prior to meals allows the insulin concentration peak to coincide with the postprandial blood glucose peak. However, many patients are unable to consistently administer regular human insulin in this fashion.²⁰ Rapid-acting insulin analogs (ie, lispro, aspart, or glulisine) provide peak serum insulin levels coinciding with peak postprandial blood glucose when administered immediately prior to meals.⁷⁻⁹ Potential benefits of the rapid-acting insulins over regular insulin include improved postprandial and total blood glucose control, as well as increased patient convenience.

In addition to traditional vials and subcutaneous syringes, numerous insulin pens or assisted-delivery devices are available (see Table 1). A recent hospital study²¹ compared patient satisfaction between insulin administered via Novo Nordisk insulin pens and traditional insulin vials and syringes. Significantly more patients using insulin pens reported that they would like to continue the delivery method at home (74% vs. 45%, $p < 0.05$) and that they would recommend the delivery method to other people (94% vs. 73%, $p < 0.05$). The external validity of these finding is limited because the study was in a hospital setting. Also, it does not address pens or assisted delivery devices produced by other manufacturers. This study does support that different delivery methods can alter patient satisfaction, and are an important consideration in selecting treatment.

Methods

We conducted a literature search to identify articles addressing each key question, searching the MEDLINE database (1950 – 2008), Cochrane Library (2008, Issue 2), and reference lists of review articles. We included trials published in English and indexed on MEDLINE prior to July 15, 2008. Whenever possible, we included only randomized, controlled

clinical trials, Cochrane systematic reviews, or meta-analyses. If published trials were available for a specific agent, we did not include trials that were available only as abstracts. When meta-analyses or Cochrane systematic reviews were available addressing the question of comparative efficacy, individual trials were not included in the evidence tables.

For this evidence-based review, our main emphasis was on published, randomized, controlled trials evaluating the efficacy of the rapid-acting insulin products in at least 20 patients for at least 8 weeks and reporting changes in A1C. Fasting, preprandial, and postprandial plasma glucoses were not reported in the clinical efficacy section, because they are not predictive of macrovascular and microvascular outcomes. Therefore, A1C is the only efficacy outcome discussed in the text and evidence tables. Outcomes were reported as either A1C change from baseline or the A1C at endpoint. Trials involving patients with gestational diabetes or pregnant patients were included if pre- or postprandial plasma glucose levels were reported. Only trials comparing individual products with each other were included for each indication. We excluded clinical trials if it was unclear which product was used, or if combinations of agents were not similar (eg, lispro/glargine versus regular/NPH).

The quality of scientific evidence was rated for each included study (refer to Appendix A for Grades of Scientific Evidence). We constructed evidence tables for all included studies (Appendix B, Evidence Tables 1 – 5), describing study design, patient selection criteria, number of patients included, treatment interventions, endpoint descriptions, significant outcomes, and grade of evidence (Appendix A). We used an evidence level of 1 for open-label trials or trials where blinding was not reported, since blinding of trials was unlikely due to time restrictions when administering rapid-acting insulins.

We identified 322 titles in our initial searches of MEDLINE and the Cochrane Library. A total of 49 trials were included in this review. Six meta-analyses compared either rapid-acting analogs to regular insulin or long-acting insulin analogs to NPH, however none of these meta-analyses were included in this review.²²⁻²⁷ One meta-analysis comparing lispro to regular insulin was excluded because it only included data from unpublished clinical trials.²³ This meta-analysis found no significant difference between the two agents regarding effects on A1C. A Cochrane review comparing rapid-acting analogs to regular insulin was excluded because pooled results for aspart and lispro were reported, rather than individual results for each agent.²⁷ Plank et al reported a summary of the Cochrane review in a separate publication, which was also excluded from this review.²⁶ A final meta-analysis comparing lispro to regular insulin was excluded because no glycemic control (ie, A1C) results were reported.²² Two meta-analyses comparing long-acting analogs to NPH were excluded because one failed to report glycemic endpoints and the other failed to report hypoglycemia as an endpoint.^{24, 25}

Clinical Efficacy

The majority of the studies performed statistical analyses on the actual A1C reported at endpoint but did not calculate a change in A1C from baseline. The change in A1C reported in Table 5 – 8 was calculated from the baseline and endpoint A1Cs reported in the trials, whenever a change in A1C was not reported in the original publication. None of the trials evaluated

morbidity as a primary outcome. Table 4 summarizes the number of studies included in this review.

All but one trial compared one of the rapid-acting insulins to regular insulin; this trial compared glulisine to lispro.²⁸ Details of each trial are presented in Appendix B, Evidence Table 1. Three trials included both type 1 and 2 diabetic patients; however, only 1 of the trials did not separate the results based on diagnosis.²⁹ This trial compared lispro and regular insulin and found no difference between groups with change in A1C at 2 months.²⁹ The trials excluded patients with microvascular complications (ie, retinopathy, nephropathy, and neuropathy), macrovascular complications, or patients who were pregnant, breastfeeding, or women practicing inadequate birth control. Each multiple daily injection trial continued therapy with a long- or intermediate-acting insulin (eg, NPH insulin). Except where indicated, insulin doses were adjusted based on patients' self-monitored blood glucose.

Table 4. Number of Included Trials

Agent	Type 1 Diabetes	Type 1 or 2 Diabetes	Type 2 Diabetes	Diabetes During Pregnancy	Type 1 Diabetes in Pediatrics
<i>Rapid-Acting</i>					
Aspart	7	—	1	3	1
Glulisine	4	—	2	—	—
Lispro	13	3	4	4	5
<i>Rapid-Acting – Continuous Subcutaneous Infusion</i>					
Aspart	1	—	—	—	—
Glulisine	1	—	—	—	—
Lispro	6	—	—	—	1

- How does glycemic control in type 1 diabetes compare between the different rapid-acting insulins?

Twenty-two trials compared a rapid-acting insulin analog with regular insulin in patients with type 1 diabetes.²⁸⁻⁵⁷ Insulin aspart was at least as effective as regular insulin in six trials.^{32-36, 57, 58} Glulisine was equally effective to lispro in one trial²⁸ and was at least as effective to regular insulin in one trial.³⁰ Lispro was at least as effective to regular insulin in 14 trials^{39, 41-47, 49, 51, 53, 54}; only 2 of the 14 trials showed an improvement in A1C reduction vs. regular insulin.^{41, 47}

Aspart insulin improved A1C by 0.08% to 0.4% from baseline. Glulisine improved A1C by 0.26% to 0.46% before meals and by 0.11% after meals. Lispro insulin improved A1C by 0.1% to 4% in 10 trials and worsened A1C 0.1% to 0.3% in 2 trials from baseline. Among all trials, regular insulin worsened A1C by 0.02% to 0.4% in 5 trials and improved A1C by 0.02% to 4.9% in 14 trials. Table 5 summarizes the effect on A1C of the studies that evaluated the rapid-acting insulins for the treatment of type 1 diabetes. The details of each study are in Appendix B, Evidence Table 1.

Aspart vs. regular insulin

Four of six trials found significantly better A1Cs at the end of treatment with aspart compared to regular insulin.^{34-36, 57} Treatment differences between groups were calculated for three of these four trials, showing significant, additional reductions in A1C with aspart ranging from 0.12% to 0.17%. Two of six trials found no difference in the A1C reported at endpoint.^{32, 33}

Glulisine vs. lispro

Dreyer et al²⁸ compared insulin glulisine to insulin lispro in a randomized, experimental trial of 672 patients. The change in A1C from baseline at 26 weeks was not significantly different for patients treated with glulisine (-0.14%) compared to lispro (-0.13%).²⁸

Glulisine vs. regular insulin

One trial compared the change in A1C of glulisine and regular insulin in type 1 diabetics over 12 weeks.³⁰ The patients who received glulisine insulin before meals demonstrated significantly greater decreases in A1C compared (-0.26%, 98.33% CI -0.02 to -0.29) to patients who received glulisine after meals (-0.11%, 98.33% CI -0.11 to -0.16, $p < 0.01$ vs. glulisine pre-meal, $p = \text{NS}$ vs. regular) or regular insulin before meals (-0.13%, 98.33% CI -0.26 to -0.01, $p < 0.01$ vs. glulisine pre-meal).³⁰

Lispro vs. regular insulin

Fourteen trials compared lispro and regular insulin in type 1 diabetic patients.^{39, 41-47, 49, 51, 53, 54} Two of these trials found significantly lower A1Cs at endpoint after 3 months (lispro: $6.34 \pm 0.1\%$ vs. regular: $6.71 \pm 0.11\%$, $p < 0.05$)⁴⁷ and 12 months of therapy (lispro: $8.12 \pm 0.85\%$ vs. regular: $8.27 \pm 0.79\%$, $p < 0.05$).⁴¹ The remaining twelve trials found no difference in the effects of lispro and regular insulin on A1C over 2-12 months of therapy.^{39, 42-46, 49, 51, 53, 54} Three of these trials did not report a baseline A1C; therefore a change in A1C could not be calculated and data were not included in Table 5.^{44, 45, 48, 52, 53} Overall, lispro insulin reduced A1C by 0.1% to 0.6% in 10 trials and increased A1C 0.1% to 0.3% in 2 trials from baseline.

Table 5. Efficacy Summary of Rapid-Acting Insulins in Type 1 Diabetes

Agent	Duration	Change in A1C (%) from baseline	Citation
Aspart	30 months	+0.01%*	Home et al, 2006 ⁵⁷
	6 months	-0.08%*	Home et al, 2000 ³⁵
	6 months	-0.12%*	Raskin et al, 2000 ³⁶
	4 months	-0.2%*	Heller et al, 2004 ³²
	15 months	-0.28%*	DeVries et al, 2003 ³³
	3 months	-0.34%*	Tamas et al, 2001 ³⁴
Glulisine post-meal	3 months	-0.11%	Garg et al, 2005 ³⁰
Glulisine pre-meal	6 months	-0.14%	Dreyer et al, 2005 ²⁸
	3 months	-0.26%	Garg et al, 2005 ³⁰
	6 months	-0.32%	Rayman et al, 2006 ⁵⁵
	6 months	-0.46%	Dailey et al, 2004 ³¹
Lispro	3 months	+0.3%*	Holleman et al, 1997 ⁴⁹
	6 months	+0.1%*	Ferguson et al, 2001 ⁴²
	12 months	-0.1%*	Garg et al, 1996 ⁵⁴
	12 months	-0.1%*	Anderson et al, 1997 ⁵²
	6 months	-0.13%	Dreyer et al, 2005 ²⁸
	4 months	-0.2%	Heller et al, 1999 ⁴⁶
	2 months	-0.2%*	Vignati et al, 1997 ⁴⁸
	12 months	-0.3%*	Lalli et al, 1999 ⁴⁷
	3 months	-0.3%*	Anderson et al, 1997 ⁵¹
	12 months	-4%*	Recasens et al, 2003 ³⁹
	3 months	-0.55%*	Annuzzi et al, 2001 ⁴¹
	3 months	-0.6%*	Valle et al, 2001 ⁴³
Regular	12 months	+0.4%*	Garg et al, 1996 ⁵⁴
	6 months	+0.3%*	Ferguson et al, 2001 ⁴²
	36 months	+0.13%*	Home et al, 2006 ⁵⁷
	6 months	+0.02%*	Home et al, 2000 ³⁵
	6 months	-0.02%*	Raskin et al, 2000 ³⁶
	3 months	0%*	Holleman et al, 1997 ⁴⁹
	12 months	0%*	Lalli et al, 1999 ⁴⁷
	2 months	-0.1%*	Vignati et al, 1997 ⁴⁸
	12 months	-0.1%*	Anderson et al, 1997 ⁵²
	3 months	-0.11%*	Tamas et al, 2001 ³⁴
	3 months	-0.13%	Garg et al, 2005 ³⁰
	15 months	-0.18%*	DeVries et al, 2003 ³³
	4 months	-0.2%*	Heller et al, 2004 ³²
	4 months	-0.2% to -0.4%	Heller et al, 1999 ⁴⁶
	3 months	-0.3%*	Anderson et al, 1997 ⁵¹
	6 months	-0.3%	Dailey et al, 2004 ³¹
	6 months	-0.35%	Rayman et al, 2006 ⁵⁵
	3 months	-0.4%*	Annuzzi et al, 2001 ⁴¹
	3 months	-0.5%*	Valle et al, 2001 ⁴³
	12 months	-4.9%*	Recasens et al, 2003 ³⁹

*Data were calculated based on baseline and endpoint results reported in the trial

- How does glycemic control in type 2 diabetes compare between the different rapid-acting insulins?

Nine trials compared a rapid-acting insulin analog and regular insulin in patients with type 2 diabetes.^{31, 37, 38, 40, 48, 50, 52, 55, 56} One trial found a significantly greater change in A1C with insulin aspart compared to regular insulin.⁵⁶ Glulisine was at least as effective as regular insulin in two trials.^{31, 55} Insulin lispro was also at least as effective as regular insulin in six trials.^{37, 38, 40, 48, 50, 52}

Aspart insulin improved A1C by 0.4% in one trial. Glulisine improved A1C by 0.32% to 0.46% in two trials. Lispro improved A1C by 0.5 to 3.2% in 6 trials. In 7 trials, regular insulin improved A1C by 0.3% to 2.7%. In one study, regular insulin increased A1C by 0.1%. Table 6 summarizes the results of the studies that evaluated the rapid-acting insulins for the treatment of type 2 diabetes. The details of each study are in Appendix B, Evidence Table 1.

Aspart vs. regular insulin

One trial evaluated aspart and regular insulin in 25 patients for 180 days.⁵⁶ Change in A1C after 180 days was significantly greater following aspart (-0.4%) compared to regular (+0.1%, $p < 0.05$).⁵⁶ A study by Bretzel et al⁵⁹ was excluded from this review due to differences in NPH basal insulin used between groups.

Glulisine vs. regular insulin

Two comparative trials evaluated glulisine and regular insulin.^{31, 55} One study compared glulisine and regular insulin for the treatment of type 2 diabetes in 876 patients for 26 weeks.³¹ The glulisine group demonstrated a decrease in A1C of -0.46% and the regular insulin group showed a decrease of -0.3%. The difference between the groups' change in A1C was significant (-0.16, 95% CI -0.26 to -0.05 %, $p = 0.0029$).³¹ In another study by Rayman et al,⁵⁵ no difference in A1C at endpoint (26 weeks) and change in A1C from baseline was seen between glulisine and regular.

Lispro vs. regular insulin

Six trials compared insulin lispro to regular insulin in patients with type 2 diabetes.^{37, 38, 40, 48, 50, 52} Four of six trials found no difference in the change in A1C over 5.5 months⁴⁰ or at A1C endpoint after 2 months,⁴⁸ 6 months,⁵⁰ and 12 months⁵² of therapy. Two other trials found significantly lower A1C after 6 months of therapy with lispro compared to therapy with regular insulin (lispro: $6.7 \pm 0.5\%$ vs. regular: $7.5 \pm 0.2\%$, $p=0.001$; lispro: $7.3 \pm 0.7\%$ vs. regular: $7.7 \pm 0.7\%$, $p<0.05$).^{37, 38}

Table 6. Efficacy Summary of Rapid-Acting Insulins in Type 2 Diabetes

Agent	Duration	Change in A1C (%) from baseline	Citation
Aspart	6 months	-0.4%	Pala et al, 2007 ⁵⁶
Glulisine	6 months	-0.32%	Rayman et al, 2007 ⁵⁵
	6 months	-0.46%	Dailey et al, 2004 ³¹
Lispro	2 months	0%*	Vignati et al, 1997 ⁴⁸
	12 months	-0.5%*	Anderson et al, 1997 ⁵²
	3 months	-0.7%*	Anderson et al, 1997 ⁵⁰
	6 months	-2.3*	Sargin et al, 2003 ³⁸
	5.5 months	-2.5 ± 0.2%	Ross et al, 2001 ⁴⁰
	6 months	-3.18%	Altuntas et al, 2003 ³⁷
Regular	6 months	+0.1%	Pala et al, 2007 ⁵⁶
	2 months	0%*	Vignati et al, 1997 ⁴⁸
	6 months	-0.3%	Dailey et al, 2004 ³¹
	6 months	-0.35%	Rayman et al, 2007 ⁵⁵
	12 months	-0.5%*	Anderson et al, 1997 ⁵²
	3 months	-0.7%*	Anderson et al, 1997 ⁵⁰
	6 months	-1.5%*	Sargin et al, 2003 ³⁸
	5.5 months	-2.3 ± 0.2%	Ross et al, 2001 ⁴⁰
	6 months	-2.66%	Altuntas et al, 2003 ³⁷

*Data were calculated based on baseline and endpoint results reported in the trial

- How does glycemic control in gestational diabetes compare between the different rapid-acting insulins?

There are no trials with glulisine insulin in patients with gestation diabetes. Three trials compared the use of lispro or aspart to regular insulin in patients with gestational diabetes.⁶⁰⁻⁶² Insulin aspart and insulin lispro were at least as effective as regular insulin. The details of these trials are presented in Appendix B, Evidence Table 2.

One study evaluated insulin aspart in gestational diabetes. Di Cianni et al⁶⁰ compared aspart, lispro, and regular insulin in patients with gestational diabetes. One hour postprandial glucose levels were significantly higher with regular insulin compared to aspart and lispro; however, the authors state that the study lacked adequate statistical power.⁶⁰ Birth weight was significantly higher with regular insulin compared to aspart and lispro groups ($p < 0.03$). A study by Pettitt et al⁶³ was excluded for review as preprandial and postprandial results were not reported.

Meccacci et al⁶¹ compared the glucose control achieved with lispro ($n = 25$) and regular insulin ($n = 24$) in patients with gestational diabetes and the glucose readings of pregnant patients without diabetes ($n = 50$). Patients were treated from the diagnosis of gestational diabetes (or pregnancy for the control group) to delivery of the child. None of the patients required therapy with NPH insulin. The overall 1-hour postprandial glucose was significantly different among the lispro insulin (108.4 ± 10.7 mg/dL), regular insulin (121 ± 13.2 mg/dL), and control groups (105.6 ± 4.7 mg/dL) with a p -value < 0.01 . However, there was no difference in the overall 2-hour postprandial glucose among the groups. The investigators found no difference

in the neonatal outcomes (ie. gestational week at deliver, Apgar score, birth weight, ponderal index) among the groups.⁶¹

Jovanoic et al⁶² compared the use of lispro (n = 19) and regular insulin (n = 22) from diagnosis of gestational diabetes to 6 weeks after delivery of the child. All patients also received NPH insulin therapy. The proportion of patients with postprandial glucose ≥ 120 mg/dL was significantly lower with lispro compared to the regular insulin group ($4\% \pm 0.49\%$ vs. $5.5\% \pm 0.47\%$, $p = 0.019$). However, the lispro and regular insulin groups demonstrated similar proportions of patients with postprandial glucoses ≥ 130 mg/dL ($1.6\% \pm 0.34\%$ vs. $1.8\% \pm 0.3\%$, $p = \text{NS}$) and ≥ 140 mg/dL ($0.65\% \pm 0.18\%$ vs. $0.69\% \pm 0.14\%$, $p = \text{NS}$). The investigators found no difference in the neonatal outcomes (ie. length, weight, percentile rank, Apgar score) among the groups.⁶²

- How does glycemic control compare between the different rapid-acting insulins in pregnant patients, other than those with gestational diabetes?

No trials evaluated the use of insulin glulisine in patients with pregestational diabetes. Two trials compared the use of lispro or aspart to regular insulin in pregnant, type 1 diabetic patients.^{64, 65} Insulin aspart and insulin lispro were both at least as effective as regular insulin in pregnant patients. The details of these trials are presented in Appendix B, Evidence Table 3.

Mathiesen et al⁶⁴ compared aspart to regular insulin in an experimental, parallel trial of 322 patients. Between treatment differences significantly favored aspart over regular insulin at the end of the first and third trimesters. No significant differences in maternal outcomes were noted between groups.⁶⁴

Persson et al⁶⁵ compared lispro (n = 16) and regular insulin (n = 17) therapy during pregnancy in type 1 diabetic patients from gestation week 15 to delivery. Postprandial plasma glucoses were similar between the groups after lunch and dinner. However, the lispro insulin group demonstrated significantly lower postprandial glucose after breakfast (117 ± 57 mg/dL) compared to the regular insulin group (154 ± 9.9 mg/dL, $p < 0.01$).⁶⁵

Three other trials evaluate use of lispro in pregnancy but do not report effects on glucose control and therefore, were not included in the evidence tables.⁶⁶⁻⁶⁸ Safety is assessed in these three trials later. No differences were observed between lispro and regular insulin with measured neonatal outcomes (including length, weight, percentile rank, Apgar score, hypoglycemia)⁶⁶ or with frequency of retinopathy in mothers.^{67, 68}

- How does glycemic control compare between the different rapid-acting insulins when treating pediatric patients?

Seven trials compared a rapid-acting insulin analog and regular insulin in pediatric patients.⁶⁹⁻⁷⁵ There are no trials comparing insulin glulisine to other rapid-acting agents in pediatric patients. Insulin aspart was equally effective to insulin lispro in one study.⁷⁴ Insulin aspart was at least as effective as regular insulin in a single trial of 30 patients.⁷³ Insulin lispro was equally effective to regular insulin in four trials.⁶⁹⁻⁷²

Weinzimer et al⁷⁴ compared insulin aspart to insulin lispro in children 4 to 18 years of age with type 1 diabetes. No significant difference was observed with changes in A1C from baseline for aspart (-0.15%) or lispro (-0.05%, 95%CI: -0.27 to 0.07); the confidence interval fell within prespecified criteria for noninferiority.⁷⁴ Cherubini et al⁷³ evaluated insulin lispro and regular insulin in children; however, A1C results were not compared to each other but were only compared to baseline. The difference in A1C from baseline was only significant for aspart treated patients (-0.5%, $p = 0.018$) but not for regular insulin.⁷³

Four published trials compared multiple daily injections of insulin lispro and regular human insulin.⁶⁹⁻⁷² The A1C response in these trials is summarized in Table 7. Change in A1C at endpoint in these trials ranged from no change to an increase of 0.5% for insulin lispro, compared with no change to a decrease of 0.4% for regular insulin ($p =$ not significant for all trials). A single trial compared insulin lispro to regular human insulin administered via continuous subcutaneous infusion.⁷⁵ Both products resulted in similar and insignificant increases in A1C compared to baseline (lispro 0.15% vs. regular 0.11%; $p =$ not significant).⁷⁵ The details of all pediatric trials are presented in Appendix B, Evidence Table 4.

Table 7. Comparative Effects of Rapid-Acting Insulins in Pediatric Patients

Agent	Duration of Treatment	Change in A1C (%) from baseline	Reference
Aspart	4 months	-0.15%	Weinzimer et al, 2008 ⁷⁴
	3 months	-0.5%*	Cherubini et al, 2006 ⁷³
Lispro - premeal	4 months	+0.5*	Ford-Adams et al, 2003 ⁷⁰
	4 months	+0.3*	Holcombe et al, 2002 ⁷²
	3 months	+0.2	Tupola et al, 2001 ⁷¹
	4 months	+0.15 \pm 0.13%	Tubiana-Rufi, 2004 ⁷⁵
	3 months	0	Deeb et al, 2001 ⁶⁹
	4 months	-0.05%	Weinzimer et al, 2008 ⁷⁴
Lispro - postmeal	3 months	+0.14*	Deeb et al, 2001 ⁶⁹
Regular human insulin	4 months	+0.11 \pm 0.63%	Tubiana-Rufi, 2004 ⁷⁵
	4 months	0*	Ford-Adams et al, 2003 ⁷⁰
	3 months	0*	Deeb et al, 2001 ⁶⁹
	4 months	-0.1*	Holcombe et al, 2002 ⁷²
	3 months	-0.1%	Cherubini et al, 2006 ⁷³
	3 months	-0.4	Tupola et al, 2001 ⁷¹

*Data were calculated based on baseline and endpoint results reported in the trial

- How does glycemic control compare between the different rapid-acting insulins when they are administered via continuous subcutaneous insulin infusion (CSII or insulin pumps)?

All of the rapid-acting insulin analogs are labeled for administration via continuous subcutaneous infusion. Seven trials comparing rapid-acting insulins to each other or to regular insulin via continuous subcutaneous infusion.⁷⁶⁻⁸² Insulin glulisine was as effective as insulin aspart in two studies.^{76, 77} Insulin aspart was equally effective to regular insulin in one study.⁷⁶ Lispro was also shown to be equally effective to regular insulin in this same study;⁷⁶ however, 5 other studies show insulin lispro to be better than regular insulin in terms of A1C reductions compared to baseline. The A1C results for these seven trials are summarized in Table 8.

Bode et al⁷⁶ compared insulin aspart, insulin lispro, and buffered regular insulin in a randomized trial. There were no significant differences in A1C effects between the three products. Hoogma et al⁷⁷ compared insulin glulisine to aspart. There were no significant differences in A1C at 12 weeks between groups.⁷⁷ Five additional trials compared insulin lispro to regular human insulin administered via continuous subcutaneous infusion.⁷⁸⁻⁸² In all five trials insulin lispro was superior to regular human insulin in terms of either total A1C at endpoint or change in A1C from endpoint.⁷⁸⁻⁸² The details of these trials are presented in Appendix B, Evidence Table 5.

A single trial compared insulin lispro to regular human insulin administered via continuous subcutaneous infusion in pediatric patients.⁷⁵ This trial was previously discussed and is included in the pediatric discussion above.

Table 8. Comparative Efficacy of Insulins via Continuous Subcutaneous Infusion

Agent	Duration of Treatment	Change in A1C (%) from baseline	Reference
Insulin Aspart	4 months	0	Bode et al, 2002 ⁷⁶
	3 months	0.1%	Hoogma et al, 2006 ⁷⁷
Insulin Glulisine	3 months	0.2%	Hoogma et al, 2006 ⁷⁷
Insulin Lispro	4 months	+0.15	Bode et al, 2002 ⁷⁶
	2 months	-0.3*	Johansson et al, 2000 ⁷⁸
	3 months	-0.34	Raskin et al, 2001 ⁸⁰
	3 months	-0.37*	Zinman et al, 1997 ⁸²
	4 months	-0.48*	Renner et al, 1999 ⁸¹
	3 months	-0.62	Melki et al, 1998 ⁷⁹
Regular Human insulin	4 months	+0.18	Bode et al, 2002 ⁷⁶
	3 months	+0.06 to -0.09	Raskin et al, 2001 ⁸⁰
	3 months	-0.03*	Zinman et al, 1997 ⁸²
	3 months	-0.09	Melki et al, 1998 ⁷⁹
	2 months	-0.1*	Johansson et al, 2000 ⁷⁸
	4 months	-0.34*	Renner et al, 1999 ⁸¹

*Data were calculated based on baseline and endpoint results reported in the trial

Adverse Drug Reactions

- How does the safety of the rapid-acting insulins compare with each other?

All of the rapid-acting insulins possess a similar adverse event profile.⁴⁻⁹ Hypoglycemia is the most common serious adverse event associated with insulins.¹ Other adverse events associated with rapid-acting insulins include allergic reactions, injection site reactions, lipodystrophy, pruritus, and rash. The incidence of these adverse events is unknown with each of the rapid-acting insulins.^{1, 4-9} With the exception of hypoglycemia, there were no significant differences in type or incidence of adverse events between the different rapid-acting insulins in the clinical trials included in this monograph. Of the trials that reported discontinuation rate, none found a significant difference among treatment groups.

Hypoglycemia results from these clinical trials will be addressed separately in the next section. Adverse events observed in the special populations (eg. pregnancy, pediatrics) are discussed separately under a separate clinical question.

- How do the rapid-acting insulins compare in terms of hypoglycemia?

Of the 29 multiple daily injection trials that evaluated hypoglycemia, 20 found no significant differences between one of the rapid-acting insulins and regular insulin.^{28-31, 33-36, 38-42, 45, 48-50, 52, 55, 56} Nine trials did find a significant difference in the rate of hypoglycemia.^{32, 37, 43, 46, 47, 51, 53, 54, 57} In most trials, hypoglycemia was more common with regular insulin than with rapid-acting insulins.

Aspart

Two of the 7 trials comparing aspart and regular insulin found more hypoglycemia in the regular insulin groups compared to aspart insulin groups.^{32, 57} Heller et al³² found more minor hypoglycemic events in the regular insulin group (38.2 events/patient-year) compared to the aspart insulin group (35.8 events/patient-year; relative risk 0.93 [95% CI 0.87 to 1], $p = 0.048$); however, the number of major hypoglycemic events was similar between the groups.³² Home et al⁵⁷ found similar results between aspart and regular insulin: a significant differences was found between groups for minor hypoglycemia ($p = 0.024$), but not for major hypoglycemic events following 36 months of treatment.⁵⁷ The other 5 trials found no significant differences in hypoglycemic events.^{33-36, 56}

Glulisine

None of the 3 trials that compared glulisine and regular insulin found a significant difference for hypoglycemic events between the groups.^{30, 31, 55} No difference in severe hypoglycemic events was observed in a comparison between glulisine and lispro.²⁸

Lispro

Seven of the 18 trials that evaluated lispro and regular insulin reported significantly more hypoglycemia in the regular insulin groups.^{37, 43, 46, 47, 51, 53, 54} Six of the seven trials were in type 1 diabetes patients. Anderson et al⁵¹ reported significantly more episodes of hypoglycemia per month for regular insulin (7.2) compared to lispro (6.4, $p < 0.001$).⁵¹ Pfutzner et al⁵³ also reported significantly more episodes of hypoglycemia per month for regular insulin (9.61) compared to lispro (8.57, $p = 0.008$). No difference in hypoglycemia was found between lispro and other rapid-acting insulins in 11 other trials.^{29, 38-42, 45, 48-50, 52}

The total number of hypoglycemia episodes was significantly more with regular insulin (1,156) compared to lispro (775) during a 4 month experimental study.⁴⁶ Garg et al⁵⁴ (12 months) also found more episodes of hypoglycemia for regular insulin patients (1,481) compared to lispro insulin patients (599, $p < 0.04$).⁵⁴ Lalli et al⁴⁷ reported a higher incidence of hypoglycemic events per patient per month for regular insulin patients compared to lispro insulin patients (11.5 vs. 7.4, $p < 0.05$). Valle et al⁴³ found that more regular insulin patients experienced severe hypoglycemia compared to the lispro insulin patients (18.7% vs. 13.8%, $p < 0.001$); however, there was no difference in the proportion of patients who reported mild hypoglycemic events.

Altuntas et al³⁷ compared regular lispro to regular in an experimental study of 60 patients. All patients were also given NPH at bedtime. The rate of hypoglycemia was significantly different between lispro (0.57%) and regular insulin (0.009%) patients.³⁷

Continuous Subcutaneous Infusion

Of the 7 continuous subcutaneous infusion studies that evaluated hypoglycemia, only one found a significant difference between agents. Bode et al⁷⁶ reported significantly less hypoglycemic episodes per patient month with insulin aspart (6.7 ± 5.4) than with lispro (10.5 ± 8.1 ; $p < 0.05$) or regular insulin (10.5 ± 8.9 ; $p < 0.05$).⁷⁶

Nocturnal Hypoglycemia

Of the 15 multiple daily injection trials that evaluated nocturnal hypoglycemia, 7 found significant differences between one of the rapid-acting insulins and regular insulin.^{32, 36, 45, 46, 49, 50, 55} The rate of nocturnal hypoglycemia was significantly greater with regular insulin than the rapid-acting insulins in these 7 studies. The other 8 trials found no differences with nocturnal hypoglycemia.^{28, 30, 31, 33, 35, 40, 42, 57}

Aspart

Five trials comparing aspart to regular insulin evaluated nocturnal hypoglycemia.^{32, 33, 35, 36, 57} Two of these trials found more nocturnal hypoglycemia in the regular insulin group.^{32, 36} Raskin et al found more major nocturnal hypoglycemia with regular insulin (8%) compared to aspart (4%, $p = 0.013$) in an experimental study of 882 patients.³⁶ The number of major nocturnal hypoglycemic events was also greater with regular insulin (2.7 events/patient year) vs. aspart (0.8 events/patient-year, $p = 0.001$) in a 4-month double-blind study. However, regular insulin was administered 0 to 5 minutes before meals, which likely contributed to the disparity in adverse events in this study.³² Three trials found no differences with nocturnal hypoglycemia in patients treated with insulin aspart or regular insulin.^{33, 35, 57}

Glulisine

Four glulisine studies (3 vs. regular, 1 vs. lispro) evaluated nocturnal hypoglycemia.^{28, 30, 31, 55} One of the 4 trials found a significantly increased rate of nocturnal hypoglycemia with regular insulin (14.5%) compared to glulisine (9.1%, $p = 0.029$).⁵⁵ Three trials found no differences with nocturnal hypoglycemia in comparisons between glulisine to regular insulin^{30, 31} or lispro²⁸.

Lispro

Of the 6 trials evaluating nocturnal hypoglycemia, 4 found significantly more events with regular insulin compared to lispro insulin.^{45, 46, 49, 50} Gale et al⁴⁵ (3 months) and Anderson et al⁵⁰ (6 months) found significantly more episodes per month or per patient per month during the trials for regular insulin compared to lispro insulin (1.8 episodes/month vs. 0.7 episodes/month, $p < 0.001$ and 0.73 vs. 0.47 episodes/patient/month, $p < 0.001$). Holleman et al⁴⁹ (12 weeks) and Heller et al⁴⁶ (4 months) found significantly more episodes during the trials for regular insulin compared to lispro insulin (312 vs. 176, $p < 0.01$ and 181 vs. 52, $p = 0.001$). No differences with nocturnal hypoglycemia occurred between insulin aspart and regular insulin in two trials.^{40, 42}

Continuous Subcutaneous Infusion

A single study by Bode et al⁷⁶ reported the incidence of nocturnal hypoglycemia in patients receiving insulin via continuous subcutaneous infusion. In this study, significantly less nocturnal hypoglycemic episodes per patient month were reported with insulin aspart (0.5 ± 0.83) than with regular insulin (0.9 ± 0.97 ; $p < 0.05$). Nocturnal hypoglycemic events associated with lispro (0.6 ± 0.61) were not significantly different from regular insulin or aspart.

- How does the safety of the rapid-acting insulins compare with each other in special populations?

Gestational Diabetes

None of three trials evaluating rapid-acting insulins in gestational diabetes included data on hypoglycemic events. Only one trial found differences in neonatal outcomes between groups. Di Cianni et al⁶⁰ found birth weight to be greater with regular insulin-treated mothers compared to aspart and lispro ($p < 0.03$). Birth weight for each group was not reported. There were no differences among the three groups for week of delivery.⁶⁰

Type 1 Diabetes and Pregnancy

Two trials reported hypoglycemic adverse events in pregnant, type 1 diabetic patients receiving either lispro, aspart, or regular insulin.^{64, 65} Persson et al⁶⁵ found no difference in the number of patients who experienced hypoglycemia symptoms, but found a greater proportion of patients in the lispro insulin group experiencing hypoglycemia (blood glucose < 54 mg/dL) compared to the regular insulin group (5.5% vs. 3.9%, $p < 0.05$). Mathiesen et al⁶⁴ found no significant difference between aspart and regular insulin in major and minor hypoglycemic events and maternal outcomes.⁶⁴

Three trials did not randomize patients to treatment groups and did not evaluate hypoglycemia. Cypryk et al⁶⁶ found no difference in maternal outcomes (ie, cesarean section, pregnancy duration) or neonatal outcomes (ie, length, weight, percentile rank, Apgar score, hypoglycemia) for patients taking lispro ($n = 25$) or regular insulin ($n = 46$). Loukovarra et al⁶⁷ found no difference in hypoglycemic events, change in retinopathy (improvement or worsening), or development of retinopathy in pregnant, type 1 diabetics taking lispro ($n = 37$) or regular insulin ($n = 35$). Bhattacharyya et al⁶⁸ reported no difference in the prevalence of retinopathy in pregnant, type 1 diabetics taking lispro ($n = 16$), regular ($n = 21$), or pork insulin ($n = 3$).

Pediatric Patients

Seven trials reported adverse event outcomes in comparative trials between lispro and regular insulin.⁶⁹⁻⁷⁵ A single trial found significantly less total hypoglycemic episodes per patient month with lispro (4) than regular insulin (4.4, $p < 0.05$).⁷² Nocturnal hypoglycemia events per patient month was also significantly less with lispro (1) compared to regular insulin (1.7, $p < 0.001$).⁷² No other significant differences in the rates of hypoglycemia or other adverse events were reported in any of these trials.

Summary

The FDA approved rapid-acting insulins include regular insulin, insulin aspart, insulin lispro, and insulin glulisine. Aspart, glulisine, and lispro are human insulin analogs, and are produced using recombinant DNA technology. The onset of action is quicker for these analogs compared to regular insulin. The rapid-acting insulins are used alone or in combination for the treatment of type 1 diabetes, type 2 diabetes, and gestational diabetes. Patients receive rapid-acting insulin analogs or regular insulin before meals to control blood glucose increases that occur during the meal.

Trials in patients with type 1 diabetes showed the following improvements in A1C with the rapid-acting insulins: aspart insulin by 0.06% to 0.34%, glulisine by 0.11% to 0.46%, lispro by 0.1% to 4%, and regular insulin by 0.08% to 4.9%. In patients with type 2 diabetes, aspart insulin improves A1C by 0.4%, glulisine improves A1C by 0.32% to 0.46%, lispro improves A1C by 0.5% to 2.7%, and regular insulin improves A1C by 0.3% to 2.3%. Comparison of reductions in A1C between rapid-acting insulins must be done with caution; no two studies were similar in study design. In general, insulins aspart, glulisine, and lispro are at least as effective as regular insulin.

The adverse events are similar among insulin products, except for hypoglycemia. Most trials with rapid-acting insulin analogs reporting hypoglycemia found similar incidences or proportions of patients with events for regular insulin compared to aspart, glulisine, or lispro insulin. Nine of 28 trials showed a significant reduction in hypoglycemic events with glulisine, lispro, or aspart compared to regular insulin.

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Document Information

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Appendix A: Grades of Scientific Evidence

- Grade 1. Evidence from randomized, blinded, placebo-controlled, clinical trials in peer reviewed journals.
- Grade 2. Non-randomized controlled trials.
- Grade 3. Non-randomized historical cohort studies. Other studies with non-experimental designs (eg, population based studies, case-control studies).
- Grade 4. Case reports, case series, abstracts of trials.
- Grade 5. Consensus of experts where data are incomplete or inconsistent.

Appendix B: Evidence Tables

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins

Evidence Table 2. Clinical Trials Evaluating the Rapid-Acting Insulins in Gestational Diabetes

Evidence Table 3. Clinical Trials Evaluating the Rapid-Acting Insulins in Pregnancy

Evidence Table 4. Clinical Trials Evaluating the Rapid-Acting Insulins in Children

Evidence Table 5. Clinical Trials Evaluating the Rapid-Acting Insulins as Subcutaneous Infusions

Appendix B: Evidence Tables

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Aspart vs. Regular						
Home et al, 2000 ³⁵ Experimental parallel: randomized, open-label, multicenter	1,065	Type 1 diabetes Adult patients (mean age 38 years), ≥ 2 years since diagnosis, and A1C ≤ 11% (mean baseline aspart 7.96%; regular insulin 7.98%)	Insulin aspart before meals (n = 707) Regular insulin 30 minutes before meals (n = 358) All patients received NPH insulin once or twice daily Duration: 6 months	Aspart > Regular A1C at 6 months, mean <ul style="list-style-type: none">Aspart: 7.88 ± 0.03%Regular: 8 ± 0.04%Difference: -0.12 (95% CI -0.03 to -0.22), p < 0.02 Change in A1C at 6 months (calculated) <ul style="list-style-type: none">Aspart: -0.08%Regular: +0.02% (no statistical comparison available) Although NPH doses were meant to remain constant throughout the trial, after correction for baseline NPH dose, patients receiving aspart received higher NPH doses than patients receiving regular insulin (difference = 0.025 units/kg, p < 0.0001) <ul style="list-style-type: none">Treatment difference adjusted for NPH dose: -0.1 (95% CI -0.004 to -0.2), p < 0.05	Discontinuation due to adverse events <ul style="list-style-type: none">Aspart: 6/707 (0.8%)Regular: 3/358 (0.8%) Major hypoglycemic events per patient year (at 6 months) <ul style="list-style-type: none">Aspart: 0.81Regular: 0.97Relative risk: 0.83 (95% CI 0.59 to 1.18), p = NS Minor hypoglycemic events per patient year (at 6 months) <ul style="list-style-type: none">Aspart: 7.64Regular: 7.54Relative risk: 1.01 (95% CI 0.89 to 1.16), p = NS Major nocturnal hypoglycemic events per patient year (at 6 months) <ul style="list-style-type: none">Aspart: 0.34Regular: 0.46Relative risk: 0.7 (95% CI 0.47 to 1.04), p = NS	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05 .

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Raskin et al, 2000 ³⁶ Experimental parallel: randomized, open-label, multicenter	882	Type 1 diabetes Adult patients (mean = 39 years), ≥ 18 months since diagnosis (mean = 16 years), A1C $\leq 11\%$ (mean baseline aspart 7.9%; regular insulin 7.95%)	Primary Study (6 months) • Insulin aspart immediately before meals (n = 596) • Regular insulin 30 minutes before meals (n = 286) 6-Month Extension • Insulin aspart immediately before meals (n = 494) • Regular insulin 30 minutes before meals (n = 220) All patients received stable doses of basal NPH at bedtime throughout the trial (< 4% also received an morning dose of NPH) Duration = 6 months (followed by an optional 6 month extension [n = 714])	Aspart > Regular A1C at 6 months • Aspart: 7.78 \pm 0.03% • Regular: 7.93 \pm 0.05% (p=0.005) Change in A1C at 6 months (calculated) • Aspart: -0.12% • Regular: -0.02% (no statistical comparison available) A1C at 12 months • Aspart: 7.78 \pm 0.04% • Regular: 7.91 \pm 0.06% (p=0.046) Change in A1C at 12 months (calculated) • Aspart: -0.12% • Regular: -0.04% (no statistical comparison available) Although NPH doses were meant to remain constant throughout the trial, after correction for baseline NPH dose, patients receiving aspart received higher NPH doses than patients receiving regular insulin (difference = 0.02 units/kg, p=0.01)	Total discontinuation at 6 months • Aspart: 44/596 (7%) • Regular: 23/286 (8%), p = NS Discontinuation due to adverse events • Aspart: 6/596 (1%) • Regular: 3/286 (1%), p = NS Major hypoglycemic events per patient year (at 6 months) • Aspart: 0.91 • Regular: 1.13, p = NS Minor hypoglycemic events per patient year (at 6 months) • Aspart: 43.44 • Regular: 45.48, p = NS Patients experiencing ≥ 1 major nocturnal hypoglycemic event • Aspart: 24/596 (4%) • Regular: 23/286 (8%), p = 0.013	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Home et al, 2006 ⁵⁷ Experimental parallel: randomized, open-label, multicenter 30-month extension study to 6-month study by Home et al. ³⁵	753	Type 1 diabetes Patients > 18 years of age, > 2 years since diagnosis, A1C ≤ 11% (mean baseline aspart 7.96%; regular insulin 7.98%)	Insulin aspart before meals (n = 567) Regular insulin 30 minutes before meals (n = 186) All patients also received NPH insulin either once or twice daily Duration: 30 month	Aspart ≥ Regular A1C at 30 months • Aspart: $8.09 \pm 0.04\%$ • Regular: $8.25 \pm 0.07\%$ • Treatment difference: -0.16, p = 0.035 A1C at 36 months • Aspart = $7.97 \pm 0.11\%$ • Regular = $8.11 \pm 0.19\%$ • Treatment difference not reported Change in A1C at 36 months (calculated) • Aspart: +0.01% • Regular: +0.13% (no statistical comparison available)	Discontinuation due to adverse events: approximately 1% in each group Major hypoglycemic events per patient year (at 36 months) • Aspart: 0.48 • Regular: 0.47, p = NS Patients experiencing minor hypoglycemic episodes • Aspart: 29% • Regular: 22%, p = 0.024 No significant differences between groups in major nocturnal hypoglycemic events	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Tamas et al, 2001 ³⁴ Experimental parallel: randomized, open-label, multicenter	423	Type 1 diabetes Patients 18 – 70 years of age, ≥ 2 years since diagnosis, A1C 7 – 10% (mean baseline aspart 8.36%; regular insulin 8.29%)	Insulin aspart 0 – 5 minutes before meals (n = 211) Regular insulin 30 minutes before meals (n = 212) All patients also received NPH insulin either once, twice, or three times daily. Duration: 12 weeks	Aspart > Regular A1C at 12 weeks <ul style="list-style-type: none"> Aspart: $8.02 \pm 0.05\%$ Regular: $8.18 \pm 0.05\%$ Treatment difference: -0.17 (95% CI -0.3 to -0.04), $p = 0.013$ Change in A1C at 12 weeks (calculated) <ul style="list-style-type: none"> Aspart: -0.34% Regular: -0.11% (no statistical comparison available) Dose and number of NPH injections increased was greater with aspart group compared to regular insulin at week 12 ($p < 0.001$). <ul style="list-style-type: none"> Treatment difference adjusted for NPH dose: -0.20 (95% CI -0.34 to -0.05), $p = 0.0073$ 	Discontinuation due to adverse events not reported Patients experiencing major hypoglycemic event <ul style="list-style-type: none"> Aspart: 15/211 (7%) Regular: 17/212 (8%) Patients experiencing minor hypoglycemic event <ul style="list-style-type: none"> Aspart: 178/211 (84%) Regular: 173/212 (81%) 	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05 .

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
DeVries et al, 2003 ³³ Experimental parallel: randomized, open-label, multicenter	362	Type 1 diabetes Patients > 18 years of age, diagnosis \geq 2 years, A1C 7 – 10% (mean baseline aspart 8.36%; regular insulin 8.4%)	Regular insulin 30 minutes before meals (n = 184) Insulin aspart immediately before meals (n = 178) All patients also received NPH insulin at bedtime. Duration: 64 weeks	Aspart = Regular A1C at 12 weeks <ul style="list-style-type: none"> Aspart: $7.98 \pm 0.05\%$ Regular: $8.12 \pm 0.05\%$ Treatment difference: -0.09 (95% CI -0.23 to -0.04), p = NS Change in A1C at 12 weeks (calculated) <ul style="list-style-type: none"> Aspart: -0.41% Regular: -0.28% (no statistical comparison available) A1C at 64 weeks <ul style="list-style-type: none"> Aspart: $8.08 \pm 0.08\%$ Regular: $8.22 \pm 0.07\%$ Treatment difference: -0.14 (95% CI -0.32 to -0.04), p = NS Change in A1C at 64 weeks (calculated) <ul style="list-style-type: none"> Aspart: -0.28% Regular: -0.18% (no statistical comparison available)	Discontinuation due to adverse events <ul style="list-style-type: none"> Aspart: 2/186 (1%) Regular: 3/181 (1.6%) Major hypoglycemic events per patient year (at 12 weeks) <ul style="list-style-type: none"> Aspart: 1.225 Regular: 1.1 Relative risk: 1.16 (95% CI 0.62 to 2.19), p = NS Minor hypoglycemic events per patient month (at 12 weeks) <ul style="list-style-type: none"> Aspart: 3.12 Regular: 3.64 Relative risk: 0.99 (95% CI 0.75 to 1.12), p = NS No differences between groups with minor and major hypoglycemic events at 64 weeks No differences between groups with rates of nocturnal hypoglycemia at 12 weeks	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Heller et al, 2004 ³² Experimental crossover: randomized, double-blind, multicenter	143	Type 1 diabetes Patients 18 – 65 years of age, ≥ 2 years since diagnosis, $A1C \leq 9\%$ (mean baseline: 7.9%)	Insulin aspart 0 – 5 minutes before meals (n = 73) Regular insulin 0 – 5 minutes before meals (n = 70) All patients also received NPH insulin either once or twice daily. Washout period of 4 weeks; all patients treated with regular insulin Duration: 4 months for each treatment arm	Aspart = Regular A1C at 4 months <ul style="list-style-type: none"> Aspart: $7.7 \pm 0.8\%$ Regular: $7.7 \pm 0.9\%$ Treatment difference: -0.105 (95% CI -0.105 to 0.17), p = NS Change in A1C at 4 months (calculated) <ul style="list-style-type: none"> Aspart: -0.2% Regular: -0.2% (no statistical comparison available)	Discontinuation due to adverse events not reported Major hypoglycemic events per patient year (at 4 months) <ul style="list-style-type: none"> Aspart: 0.85 Regular: 1.11 Relative risk: 0.72 (95% CI 0.47 to 1.09), p = NS Minor hypoglycemic events per patient year (at 4 months) <ul style="list-style-type: none"> Aspart: 35.8 Regular: 38.2 Relative risk: 0.93 (95% CI 0.87 to 1.00), p = 0.048 Major nocturnal hypoglycemic events per patient year (at 4 months) <ul style="list-style-type: none"> Aspart: 0.8 Regular: 2.7 Relative risk: 0.28 (95% CI 0.13 to 0.59), p = 0.001 	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Pala et al, 2007 ⁵⁶ Experimental crossover: randomized, open-label	25	Type 2 diabetes Patients 30 – 65 years of age, ≥ 5 years since diagnosis, A1C $> 7.5\%$ despite treatment with oral hypoglycemic agents (mean baseline: 7.3%)	Patients were randomized to 1 of 2 groups and were treated for 90 days before crossover <ul style="list-style-type: none"> Insulin aspart 0.1 units/kg, immediately before meals Regular insulin 0.1 units/kg, 30 minutes before meals All patients received metformin 500 mg three times a day after meals Washout period undefined Duration: 180 days	Aspart \geq Regular A1C at 180 days <ul style="list-style-type: none"> Aspart: 7.3\pm0.7% Regular: 7.9\pm0.05% (no statistical comparisons made) Change in A1C at 180 days <ul style="list-style-type: none"> Aspart: -0.4% Regular: 0.1% (p < 0.05) 	Discontinuations due to adverse events not reported No severe hypoglycemic events reported Mild hypoglycemic events per month <ul style="list-style-type: none"> Aspart: 2.2 Regular: 2.3, p = NS 	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Glulisine vs. Regular						
Garg et al, 2005 ³⁰ Experimental parallel: randomized, open-label, multi-center	860	Type 1 Diabetes Patients ≥ 18 years of age, > 1 year of insulin therapy, A1C 6 to 11% (baseline range of 7.6 to 7.7%)	Insulin glulisine 0 – 15 before or after meals (n = 286) Insulin glulisine immediately after a meal or 20 minutes after starting a meal (n = 296) Regular insulin 30 to 45 minutes before meals (n = 278) All patients received doses of basal insulin glargine throughout the trial Duration: 12 weeks	Premeal Glulisine > Postmeal Glulisine, Regular Postmeal Glulisine = Regular Change in A1C at 12 weeks <ul style="list-style-type: none">• Premeal glulisine: -0.26%, p = 0.02 vs. regular, p = 0.006 vs. postmeal glulisine• Postmeal glulisine: -0.11%, p = NS vs. regular• Regular: -0.13%	Discontinuation due to adverse events: <ul style="list-style-type: none">• Premeal glulisine: 3/286 (1%)• Postmeal glulisine: 3/296 (1%)• Regular: 4/278 (1.4%) Severe hypoglycemic events per patient month (at 12 weeks) <ul style="list-style-type: none">• Premeal glulisine: 0.05• Postmeal glulisine: 0.05• Regular: 0.13• p = NS, all comparisons Symptomatic hypoglycemic events per patient month (at 12 weeks) <ul style="list-style-type: none">• Premeal glulisine: 3.46• Postmeal glulisine: 3.71• Regular: 3.49• p = NS, all comparisons Nocturnal hypoglycemic events per patient month (at 12 weeks) <ul style="list-style-type: none">• Premeal glulisine: 0.64• Postmeal glulisine: 0.71• Regular: 0.71• p = NS, all comparisons	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Rayman et al, 2007 ⁵⁵ Experimental parallel: randomized, open-label, multi-center	890	Type 2 diabetes Patients ≥ 18 years of age, > 6 months of continuous insulin therapy since diagnosis. A1C 6 – 11% (mean baseline glulisine 7.57%; regular 7.51%)	Insulin glulisine, administration time relative to meals not defined (n = 448) Regular insulin, administration time relative to meals not defined (n = 442) All patients received twice daily doses of basal NPH Patients were allowed to continue stable doses of oral hypoglycemic agents except glitazones, repaglinide, and nateglinide Duration: 26 weeks	Glulisine = Regular A1C at 26 weeks • Glulisine: $7.25 \pm 0.95\%$ • Regular: $7.19 \pm 0.9\%$ (p = NS) Change in A1C at 26 weeks • Glulisine: -0.32% • Regular: -0.35% (p = NS)	Discontinuation due to adverse events • Glulisine: 9/448 (2%) • Regular: 3/442 (0.6%) Patients experiencing > 1 severe hypoglycemic event (at 26 weeks) • Glulisine: 2/448 (0.5%) • Regular: 7/442 (1.6%), p = NS Patients experiencing nocturnal hypoglycemic event • Glulisine: 39/448 (9.1%) • Regular: 63/442 (14.5%), p = 0.029	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Dailey et al, 2004 ³¹ Experimental parallel: randomized, open-label, multicenter	876	<p>Type 2 diabetes</p> <p>Patients ≥ 18 years of age, insulin therapy ≥ 6 months, A1C 6-11% (mean baseline glulisine 7.57%; regular insulin 7.5%)</p> <p>Baseline – glulisine patients were significantly older than regular insulin patients (58.9 ± 10.20 years vs. 57.7 ± 9.9 years, $p=0.04$). Glulisine patients had diabetes significantly longer than regular insulin patients (14.7 ± 8.12 years vs. 13.4 ± 7.55 years, $p=0.02$)</p>	<p>Insulin glulisine 0 – 15 minutes before breakfast and dinner (n = 435)</p> <p>Regular insulin 30 – 40 minutes before breakfast and dinner (n = 441)</p> <p>All patients also received NPH insulin at bedtime and were allowed to continue oral hypoglycemic medications</p> <p>Duration: 26 weeks</p>	<p>Glulisine > Regular</p> <p>A1C at 26 weeks</p> <ul style="list-style-type: none"> Glulisine: 7.08% Regular: 7.19%, $p = 0.0341$ <p>Change in A1C at 26 weeks</p> <ul style="list-style-type: none"> Glulisine: -0.46% Regular: -0.3% Treatment difference: -0.16 (95% CI -0.26 to -0.05 %), $p = 0.0029$ 	<p>Discontinuation due to adverse events</p> <ul style="list-style-type: none"> Glulisine: 5/435 (1.1%) Regular: 6/441 (1.3%) <p>Patients experiencing ≥ 1 hypoglycemic event</p> <ul style="list-style-type: none"> Glulisine: 51.7% Regular: 53.6%, $p = NS$ <p>Patients experiencing ≥ 1 nocturnal hypoglycemic event</p> <ul style="list-style-type: none"> Glulisine: 21.4% Regular: 24.5%, $p = NS$ 	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05 .

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Glulisine vs. Lispro						
Dreyer et al, 2005 ²⁸ Experimental parallel: randomized, open-label, multicenter	672	Type 1 diabetes Patients ≥ 18 years of age, > 1 year of continuous insulin therapy since diagnosis. Onset of diabetes was before patient was 40 years of age. A1C 6 – 11% (mean baseline: lispro 7.58%; glulisine: 7.6%)	Insulin glulisine 0 – 15 before meals (n = 339) Insulin lispro 0 – 15 minutes before meals (n = 333) All patients received injection of glargine once daily Duration: 26 weeks	Glulisine = Lispro A1C at 26 weeks <ul style="list-style-type: none">Glulisine: 7.46±0.9%Lispro: 7.45±0.09% (p value not reported) Change in A1C at 26 weeks <ul style="list-style-type: none">Glulisine: -0.14%Lispro: -0.13% (p = NS)	Discontinuation due to adverse events <ul style="list-style-type: none">Glulisine: 2/339 (0.3%)Lispro: 3/333 (0.9%, p value not reported) Severe hypoglycemic events per patient month (at 26 weeks) <ul style="list-style-type: none">Glulisine: 0.03Lispro: 0.02 (p value not reported) Symptomatic hypoglycemic events per patient month (at 26 weeks) <ul style="list-style-type: none">Glulisine: 3.64Lispro: 3.48 (p value not reported) Nocturnal hypoglycemic events per patient month (at 26 weeks) <ul style="list-style-type: none">Glulisine: 0.55Lispro: 0.55 (p value not reported)	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Lispro vs. Regular						
Valle et al, 2001 ⁴³ Experimental parallel: randomized, open-label	1,184	Type 1 diabetes Patient (mean age 38.7 years) with A1C ≥ 7.5% (mean baseline 8.7%), insulin therapy for at least 60 days	Insulin lispro immediately before meals (n = 586) Regular insulin 30 minutes before meals (n = 598) All patients also received NPH insulin up to 3 times a day Duration: 3 months	Lispro = Regular A1C at 3 months • Lispro: 8.1 ± 1.5% • Regular: 8.2 ± 1.5%, p = NS Change in A1C at 3 months (calculated) • Lispro: -0.6% • Regular: -0.5% (no statistical comparison available)	Discontinuation due to adverse events not reported Total hypoglycemic episodes per patient per month • Lispro: 1.8±1.8 • Regular: 1.8±1.7, p = NS Severe hypoglycemic episodes (% of total episodes) • Lispro: 13.8 • Regular: 18.7, p < 0.001	1
Anderson et al, 1997 ⁵¹ Experimental crossover: randomized, double-blind, multicenter	1,008	Type 1 diabetes Patients 12 – 70 years of age, A1C requirement not specified (mean baseline 8.5%). Patient diagnosed with diabetes for an average of approximately 12 years.	Insulin lispro immediately before meals Regular insulin 30-45 minutes before meals All patients also received basal NPH or Ultralente insulin at least once a day. Duration: Patients treated for 3 months and immediately crossed-over to other treatment arm for an additional 3 months	Lispro = Regular A1C after 3 months of treatment • Lispro: 8.2 ± 0.1% (p < 0.01 vs. baseline) • Regular: 8.2 ± 0.1% (p < 0.01 vs. baseline) • p = NS between groups Change in A1C at 3 months (calculated) • Lispro: -0.3% • Regular: -0.3% (no statistical comparison available)	Discontinuation due to adverse events not reported; authors reported no difference in discontinuation between groups Hypoglycemic events at endpoint • Lispro: 6.4 ± 0.2 events/30 days • Regular: 7.2 ± 0.3 events/30 days, p < 0.001	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Holleman et al, 1997 ⁴⁹ Experimental crossover: randomized, double-blind, multicenter	199	Type 1 diabetes Patients 18 – 65 years of age, A1C < 1.5 times the top normal range of the local laboratory (mean baseline 7.3%)	Insulin lispro immediately before meals Regular insulin 30 minutes before meals Duration: Patients treated for 12 weeks and immediately crossed-over to other treatment arm for an additional 12 weeks	Lispro = Regular A1C after 12 weeks of treatment • Lispro: $7.6 \pm 1.3\%$ • Regular: $7.5 \pm 1.2\%$, p = NS Change in A1C at 12 weeks (calculated) • Lispro: +0.3% • Regular: 0% (no statistical comparison available)	Discontinuation due to adverse events not reported Total hypoglycemic events • Lispro: 2,249 events • Regular: 2,433 events, p = NS Nocturnal hypoglycemic events • Lispro: 176 events • Regular: 312 events, p < 0.001	1
Heller et al, 1999 ⁴⁶ Experimental crossover: randomized, open-label, multicenter	135	Type 1 diabetes Adults (mean age 37 years lispro; 39 years regular), diagnosis ≥ 2 years, A1C < 8% (baseline mean: lispro 6.2%; regular 6.4%)	Insulin lispro immediately before meals Regular insulin 30 minutes before meals All patients also received basal NPH. Duration: Patients treated for 4 months and immediately crossed-over to other treatment arm for an additional 4 months	Lispro = Regular A1C after 4 months of treatment Period 1 • Lispro: $6 \pm 0.9\%$ • Regular: $6.2 \pm 0.8\%$, p = NS Period 2 • Lispro: $6.4 \pm 1.1\%$ • Regular: $6.4 \pm 1.1\%$, p = NS Change in A1C from start of treatment to end of treatment period Period 1 • Lispro: -0.2% • Regular: -0.2% Period 2 • Lispro: -0.2% • Regular: -0.4%, p value not reported	Discontinuation due to adverse events not reported Hypoglycemia Period 1 • Lispro: 775 episodes • Regular: 1,156 episodes, p = 0.04 Period 2 (due to significant period and treatment-period interaction, values were not compared) • Lispro: 883 episodes • Regular: 702 episodes Nocturnal hypoglycemia, reported for Period 1 only • Lispro: 52 episodes • Regular: 181 episodes, p = 0.001	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Pfutzner et al, 1996 ⁵³ Experimental crossover: randomized, open-label	107	Type 1 diabetes Patients 18 – 65 years of age, insulin therapy for at least 2 months, no A1C criteria specified (baseline A1C not reported)	Insulin lispro, dosing interval undefined Regular insulin, dosing interval undefined All patients also received NPH insulin as basal insulin Duration: Patients treated for 3 months and immediately crossed-over to other treatment arm for an additional 3 months	Lispro = Regular A1C after 3 months of treatment • Lispro: $7.42\% \pm 0.12\%$ • Regular: $7.47 \pm 0.12\%$, p = NS	One discontinuation due to adverse event (treatment group not reported) Total hypoglycemic episodes per month • Lispro: 8.57 episodes/month • Regular: 9.61 episodes/month, p = 0.008	1
Gale et al, 2000 ⁴⁵ Experimental crossover: randomized, double-blind, multicenter	93	Type 1 diabetes Adult patients (median age 35 years), diagnosis at age < 40 years old, A1C < 1.5 times upper limit of normal nondiabetic patient (baseline A1C not reported)	Insulin lispro immediately before meals Regular insulin 30 minutes before meals All patients also received basal NPH once at night. Duration: Patients treated for 3 months and immediately crossed-over to other treatment arm for an additional 3 months	Lispro = Regular A1C after 3 months of treatment • Lispro: $7.5 \pm 1.1\%$ • Regular: $7.4 \pm 1.1\%$, p = NS	Discontinuation due to adverse events (hypoglycemia) • Lispro: 0/93 • Lispro: 2/93 (2.1%) Total hypoglycemic events • Lispro: 2.6 ± 3 events/30 days • Regular: 3.1 ± 4.4 events/days, p = NS Total nocturnal hypoglycemic events • Lispro: 0.7 ± 1.6 events/30 days • Regular: 1.8 ± 3.1 events/days, p < 0.001	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Annuzzi et al, 2001 ⁴¹ Experimental crossover: randomized, open-label	85	Type 1 diabetes Patients 18 – 50 years of age, diagnosis for at least 2 years and before age 35 years old, A1C 7.5 – 10% (mean baseline 8.67%)	Insulin lispro immediately before meals Regular insulin 30 – 45 minutes before meals All patients also received NPH insulin up to 3 times a day Patients treated for 3 months and immediately crossed-over to other treatment arm for an additional 3 months	Lispro > Regular A1C after 3 months of treatment • Lispro: $8.12 \pm 0.85\%$ • Regular: $8.27 \pm 0.79\%$, $p < 0.05$ Change in A1C at 3 months (calculated) • Lispro: -0.55% • Regular: -0.4% (no statistical comparison available)	Discontinuation due to adverse events not reported All hypoglycemic events per month per patient (at 3 months) • Lispro: 256 episodes/month/patient • Regular: 204 episodes/month/patient, $p = \text{NS}$ Major hypoglycemic events per month per patient (at 3 months) • Lispro: 0.7 episodes/month/patient • Regular: 1 episodes/month/patient, $p = \text{NS}$	1
Lalli et al, 1999 ⁴⁷ Experimental parallel: randomized, open-label	56	Type 1 diabetes Patients (mean age 34 years), A1C 6 – 7.5% (mean baseline lispro 6.6%; regular 6.7%)	Insulin lispro immediately before meals (n = 28) Regular insulin 10 – 40 minutes before meals (n = 28) All patients also received NPH insulin at bedtime. NPH was also given to 36 patients at lunchtime while on regular insulin Duration: 12 months	Lispro > Regular A1C after 12 months of treatment • Lispro: $6.3 \pm 0.1\%$ • Regular: $6.7 \pm 0.11\%$ • Difference: $0.37 \pm 0.04\%$, $p < 0.05$ Change in A1C at 12 months (calculated) • Lispro: -0.3% • Regular: 0% (no statistical comparison available)	Discontinuation due to adverse events not reported Total hypoglycemic events per patient month (at 12 months) • Lispro: 7.4 ± 0.5 • Regular: 11.5 ± 1.2 ($p < 0.05$)	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Recasens et al, 2003 ³⁹ Experimental parallel: randomized, open-label	45	Type 1 diabetes Adults (mean age 22.4 years regular; 24.4 years lispro) new diagnosis, A1C not specified (mean lispro 10.5%; mean regular 11.4%)	Insulin lispro immediately before meals (n = 22) Regular insulin 30 minutes before meals (n = 23) All patients also received NPH insulin 1 – 2 times daily. Duration: 12 months	Lispro = Regular A1C after 12 months of treatment (estimated from table) • Lispro: 6.5% • Regular: 6.5%, p= NS Change in A1C at 12 months (calculated) • Lispro: -4% • Regular: -4.9% (no statistical comparison available)	Discontinuation due to adverse events not reported No major hypoglycemic events reported in any group Minor hypoglycemic events per week (at 12 months) • Lispro: 0.3 episodes/week • Regular: 0.8 episodes/week, significance not reported	1
Garg et al, 1996 ⁵⁴ Experimental parallel: randomized, open-label	37	Type 1 diabetes Patients 13 to 34 years of age, A1C criteria not specified (mean baseline: lispro 9.1%; regular 8.4%)	Insulin lispro 5 – 15 minutes before meals (n = 16) Regular insulin 20 – 40 minutes before meals (n = 21) All patients also received basal NPH (twice daily) or Ultralente insulin once or twice daily Duration: 12 months	Lispro = Regular A1C after 12 months of treatment • Lispro: $9 \pm 0.9\%$ • Regular: $8.8 \pm 1.4\%$, p = NS Change in A1C at 12 months (calculated) • Lispro: -0.1% • Regular: +0.4% (no statistical comparison available)	Discontinuation due to adverse events not reported Total hypoglycemic events • Lispro: 599 events • Regular: 1,481 events, p < 0.04	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Ferguson et al, 2001 ⁴² Experimental crossover: randomized, open-label	33	Type 1 diabetes Patients 19 – 65 years of age, ≥ 5 years since diagnosis, A1C < 10 – 13% (baseline mean: 9%), ≥ 2 episodes of severe hypoglycemia in previous 2 years	Insulin lispro immediately before meals Regular insulin 30 minutes before meals All patients also received basal NPH once or twice daily Duration: Patients treated for 24 weeks and immediately crossed-over to other treatment arm for an additional 24 weeks	Lispro = Regular A1C after 24 weeks of treatment <ul style="list-style-type: none"> Lispro: $9.1 \pm 0.83\%$ Regular: $9.3 \pm 1\%$, p = NS Change in A1C at 24 weeks (calculated) <ul style="list-style-type: none"> Lispro: +0.1% Regular: +0.3% (no statistical comparison available)	Discontinuation due to adverse events not reported Total hypoglycemic events <ul style="list-style-type: none"> Lispro: 1,156 events Regular: 1,115 events, p = NS Total nocturnal hypoglycemic events <ul style="list-style-type: none"> Lispro: 25 events Regular: 47 events, p = NS 	1
Beisswenger et al, 2001 ⁴⁴ Experimental crossover: randomized, double-blind	21	Type 1 diabetes Patients 15-65 years of age, A1C criteria not specified (baseline A1C not reported)	Insulin lispro immediately before meals Regular insulin 10 – 40 minutes before meals All patients also received NPH, lente, or Ultralente insulin. Duration: Patients treated for 2 months and immediately crossed-over to other treatment arm for an additional 2 months	Lispro = Regular A1C after 2 months of treatment <ul style="list-style-type: none"> Lispro: $7.59 \pm 0.9\%$ Regular: $7.83 \pm 0.86\%$, p = NS 	Discontinuations and hypoglycemia not reported	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Vignati et al, 1997 ⁴⁸ Experimental crossover: randomized, open-label, multi-center	707	Type 1 diabetes (n = 379) Type 2 diabetes (n = 328) Patients > 18 years of age, insulin therapy for at least 2 months, excluded use of oral hypoglycemic agents, A1C not specified (mean A1C Type 1: 8%; mean A1C Type 2: 8.1%)	Insulin lispro immediately before breakfast and dinner Regular insulin before breakfast and dinner (timing of dose undefined) All patients also received NPH insulin before breakfast and dinner. Duration: Patients treated for 2 months and immediately crossed-over to other treatment arm for an additional 2 months	Type 1 Diabetes Lispro = Regular A1C at 2 months • Lispro: $7.8 \pm 1.4\%$ • Regular: $7.9 \pm 1.5\%$, p = NS Change in A1C after 2 months (calculated) • Lispro: -0.2% • Regular: -0.1%, p = NS Type 2 Diabetes Lispro = Regular A1C at 2 months • Lispro: $8.1 \pm 1.4\%$ • Regular: $8.1 \pm 1.4\%$, p = NS Change in A1C after 2 months (calculated) • Lispro: 0% • Regular: 0% (no statistical comparison available)	Discontinuation due to adverse events not reported <i>Type 1 Diabetes</i> Total hypoglycemic episodes per month • Lispro: 4.6 ± 5.5 • Regular: 4.6 ± 5 , p = NS <i>Type 2 Diabetes</i> Total hypoglycemic episodes per month • Lispro: 1.9 ± 3.9 • Regular: 1.9 ± 3.7 , p = NS	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Anderson et al, 1997 ⁵² Experimental parallel: randomized, open-label, multicenter	631	Type 1 diabetes (n = 379) Type 2 diabetes (n = 328) Patients with Type 1 diabetes (age 12-70 years) or with Type 2 diabetes (ages 35 to 70 years), insulin therapy for at least 2 months, excluded use of oral hypoglycemic agents or insulin infusion devices, A1C not specified (mean baseline Type 1: lispro 8.2%; regular 8.2%. mean baseline Type 2: lispro 8.7%; regular 8.9%)	Insulin lispro immediately before meals (n = 307) Regular insulin 30 – 45 minutes before meals (n = 324) All patients also received Ultralente or NPH insulin (frequency undefined) Duration: 12 months	Type 1 Diabetes Lispro = Regular A1C at 12 months • Lispro: $8.1 \pm 0.1\%$ • Regular: $8.3 \pm 0.1\%$, $p < 0.05$ vs. lispro Change in A1C after 12 months (calculated) • Lispro: -0.1% • Regular: -0.1% (no statistical comparison available) Type 2 Diabetes Lispro = Regular A1C at 12 months • Lispro: $8.2 \pm 0.1\%$ • Regular: $8.4 \pm 0.1\%$, $p = NS$ Change in A1C after 12 months (calculated) • Lispro: -0.5% • Regular: -0.5% (no statistical comparison available)	Discontinuation due to adverse events not reported <i>Type 1 Diabetes</i> Hypoglycemic episodes/month • Lispro: 4.4 ± 0.5 • Regular: 4.5 ± 0.4 , $p = NS$ <i>Type 2 Diabetes</i> Hypoglycemic episodes/month • Lispro: 1.5 ± 0.2 • Regular: 1.6 ± 0.3 , $p = NS$	1
Skrha et al, 2002 ²⁹ Experimental crossover: randomized, open-label	62	Type 1 diabetes (n = 55) Type 2 diabetes (n = 7) Patients (mean age 35.7 years), insulin therapy for at least 2 months, A1C not specified (mean baseline: 7.5%)	Insulin lispro immediately before meals Regular insulin 30 minutes before meals All patients also received NPH insulin once or twice daily Duration: Patients treated for 2 months and immediately crossed-over to other treatment arm for an additional 2 months	Lispro = Regular A1C after 2 months of treatment • Lispro: $7.6 \pm 1.5\%$ • Regular: $7.4 \pm 1.5\%$, significance not reported Change in A1C after 2 months • Lispro: $+0.1 \pm 0.9\%$ • Regular: $0 \pm 1\%$, $p = NS$	Discontinuation due to adverse events not reported Patients reporting hypoglycemia • Lispro: 41/62 (66%) • Regular: 39/62 (63%), $p = NS$	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Anderson et al, 1997 ⁵⁰ Experimental crossover: randomized, open-label, multicenter	722	Type 2 diabetes Patients ages 35 to 85 years, insulin therapy ≥ 2 months, excluded use of oral hypoglycemic agents, A1C not specified (mean baseline A1C 8.9%)	Insulin lispro immediately before breakfast and dinner Regular insulin 30 to 45 minutes before breakfast and dinner All patients also received NPH or Ultralente insulin 1-2 times daily. Duration: Patients treated for 3 months and immediately crossed-over to other treatment arm for an additional 3 months	Lispro = Regular A1C at end of 3 months of treatment • Lispro: $8.2 \pm 0.1\%$ • Regular: $8.2 \pm 0.1\%$, p = NS Change in A1C at 3 months (calculated) • Lispro: -0.7% • Regular: -0.7% (no statistical comparison available)	Discontinuation due to adverse events not reported Total hypoglycemia at endpoint (episodes per 30 days per patient) • Lispro: 2.67 ± 0.17 • Regular: 2.79 ± 0.17 , p = NS Total nocturnal hypoglycemia at endpoint (episodes per 30 days per patient) • Lispro: 0.47 ± 0.05 • Regular: 0.73 ± 0.07 , p < 0.001	1
Ross et al, 2001 ⁴⁰ Experimental parallel: randomized, open-label, multicenter	148	Type 2 diabetes Patients (age undefined) with uncontrolled diabetes despite oral hypoglycemic therapy, A1C no greater than 130% of upper normal range (mean baseline: lispro 10.7%; mean regular 10.6%)	Insulin lispro immediately before breakfast and dinner (n = 70) Regular insulin 30 to 45 minutes before breakfast and dinner (n = 78) All patients also received NPH insulin before breakfast and supper Duration: 5.5 months	Lispro = Regular A1C at end of 5.5 months of treatment • Lispro: $8 \pm 0.1\%$ • Regular: $8 \pm 0.1\%$, p = NS Change in A1C at 5.5 months • Lispro: $-2.5 \pm 0.2\%$ • Regular: $-2.3 \pm 0.2\%$, p = NS	Discontinuation due to adverse events: 1/148 (0.7%) Total hypoglycemia (episodes per 30 days) • Lispro: 1.8 ± 0.3 • Regular: 1.7 ± 0.3 , p = NS Total nocturnal hypoglycemia (episodes per 30 days) • Lispro: 0.08 • Regular: 0.16, p = NS	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 1. Clinical Trials Evaluating the Rapid-Acting Insulins (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Altuntas et al, 2003 ³⁷ Experimental parallel: randomized, open-label, multicenter	60	Type 2 diabetes Patients (mean age 53.8 to 54.8 years), uncontrolled diabetes despite oral hypoglycemic therapy, A1C not specified (mean lispro + NPH 10.1%; mean lispro + metformin 9.4%; mean regular + NPH 9.6)	Insulin lispro immediately before meals plus NPH at bedtime (n = 20) Insulin lispro immediately before meals plus metformin twice daily (n = 20) Regular insulin 30 to 45 minutes before meals plus NPH at bedtime (n = 20) Duration: 6 months	Lispro > Regular (Lispro + metformin results excluded) A1C at 6 months • Lispro: $6.7 \pm 0.5\%$ • Regular: $7.5 \pm 0.2\%$, p = 0.013 Change in A1C at 6 months • Lispro: -3.18%, p = 0.001 vs. baseline • Regular: -2.66%, p = 0.008 vs. baseline	Discontinuation due to adverse events not reported Total hypoglycemia • Lispro: 0.57% • Regular: 0.009%, p = 0.012	1
Sargin et al, 2003 ³⁸ Experimental parallel: randomized, open-label, multicenter	56	Type 2 diabetes Patients (age undefined) currently treated with insulin, A1C > 8% (mean lispro 9.6%; mean regular 9.2%)	Insulin lispro immediately before meals plus NPH at lunch and bedtime (n = 28) Regular insulin 30 to 45 minutes before meals plus NPH at bedtime (n = 27) Duration: 6 months	Lispro > Regular A1C at 6 months • Lispro: $7.3 \pm 0.7\%$ • Regular: $7.7 \pm 0.7\%$, p < 0.05 Change in A1C at 6 months (calculated) • Lispro: -2.3 • Regular: -1.5%, p value not reported	Discontinuation due to adverse events not reported Total hypoglycemia (episodes per 30 days) • Lispro: 1.6 ± 1 • Regular: 1.9 ± 0.8 , p = NS	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 2. Clinical Trials Evaluating the Rapid-Acting Insulins in Gestational Diabetes

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Di Cianni et al, 2007 ⁶⁰ Experimental, parallel: randomized, open-label	96	Gestational diabetes Women who failed to achieve postprandial glycemic goals on diet treatment.	Insulin aspart before meals (n = 31) Insulin lispro before meals (n = 33) Regular insulin, administration time relative to meals not defined (n = 32) Bedtime NPH insulin given to 57 patients Duration: Until the end of pregnancy, 38 th week gestation	Aspart = Lispro = Regular Authors state that this study lacks adequate statistical power No differences in A1C and fasting plasma glucose were detected between groups 1 hour postprandial glucose levels after breakfast • Lispro: 118.9 mg/dL, p < 0.05 vs. regular • Aspart: 120.24 mg/dL, p < 0.05 vs. regular • Regular: 135.1 mg/dL	No patient experienced hypoglycemic episodes. Neonatal outcomes: Birth weight was significantly higher with regular insulin compared to aspart and lispro groups, p < 0.03	1
Mecacci et al, 2003 ⁶¹ Experimental parallel: randomized, open-label, single center	49	Gestational Diabetes Pregnant, diagnosed between weeks 25-32 gestation, failed to achieve glycemic goals after 1 week of diet modifications	Insulin lispro immediately before meals (n = 25) Regular insulin 15 minutes before meals (n = 24) Healthy pregnant volunteer control group (n = 50) No patients required NPH insulin Duration: from diagnosis to delivery	Lispro = Regular Preprandial glucose levels, p < 0.01 between groups • Lispro: 73.4 ± 8.1 mg/dL • Regular: 74.3 ± 8.6 mg/dL • Control: 62.7 ± 4 mg/dL 1-hour postprandial glucose, p < 0.01 between groups • Lispro: 108.4 ± 10.7 mg/dL • Regular: 121 ± 13.2 mg/dL • Control: 105.6 ± 4.7 mg/dL 2-hour postprandial glucose, p = NS between groups • Lispro: 93.6 ± 11.1 mg/dL • Regular: 97.9 ± 12.5 mg/dL • Control: 91.7 ± 5.5 mg/dL	No discontinuation due to adverse events reported Neonatal outcomes: No significant difference among groups for gestational week at deliver, Apgar score, birth weight, ponderal index	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 2. Clinical Trials Evaluating the Rapid-Acting Insulins in Gestational Diabetes (continued) 52

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Jovanovic et al, 1999 ⁶² Experimental parallel: randomized, open-label, single center	41	Gestational Diabetes Pregnant (mean age lispro group 34.2 years; mean age regular group, $p < 0.01$), diagnosed between weeks 14-32 gestation, failed to achieve glycemic goals with diet and exercise	Insulin lispro 5 minutes before meals (n = 19) Regular insulin 30 minutes before meals (n = 22) All patients also received NPH insulin. Patients received dextrose and insulin infusions during delivery Duration: from diagnosis of gestational diabetes mellitus to 6 weeks postpartum	Lispro \geq Regular Proportion of postprandial blood glucose determinations ≥ 120 mg/dL <ul style="list-style-type: none"> Lispro = 4 ± 0.49 % Regular = 5.5 ± 0.47 %, $p = 0.019$ Proportion of postprandial blood glucose determinations ≥ 130 mg/dL <ul style="list-style-type: none"> Lispro = 1.6 ± 0.34 % Regular = 1.8 ± 0.3 %, $p = \text{NS}$ Proportion of postprandial blood glucose determinations ≥ 140 mg/dL <ul style="list-style-type: none"> Lispro = 0.65 ± 0.18 % Regular = 0.69 ± 0.14 %, $p = \text{NS}$ Preprandial glucose levels not recorded	No discontinuation due to adverse events reported Neonatal outcomes: No significant difference among groups for length, weight, percentile rank, Apgar scores	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05 .

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 3. Clinical Trials Evaluating the Rapid-Acting Insulins in Pregnancy

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Mathiesen et al, 2007 ⁶⁴ Hod et al, 2008 ⁸³ Experimental parallel: open-label, multicenter Note: manuscript reported in multiple journals	322	Type 1 diabetes Patients ≥ 18 years of age, > 1 year since diagnosis, $A1C \leq 8\%$. Patients were pregnant or planning to become pregnant.	Insulin aspart immediately before meals (n = 157) Regular insulin 30 minutes before meals (n = 165) All patients received doses of basal NPH one to four times a day Duration: maximum duration of participation was 22 months	Aspart \geq Regular (at end of first and third trimesters) Mean postprandial plasma glucose differences at end of first trimester: -0.75 (95% CI: -1.25 to -0.25), p = 0.003 favoring aspart Mean postprandial plasma glucose differences at end of third trimester: -0.4 (95% CI: -0.8 to -0.01), p = 0.044 favoring aspart Mean A1C difference at end of second trimester: -0.04% (95% CI -0.18 to 0.11), p = NS Mean A1C difference at end of third trimester: -0.08% (95% CI -0.23 to 0.06), p = NS	Discontinuation due to adverse events • Aspart: 14/157 (9%) • Regular: 17/165 (10%) Major hypoglycemic events per patient year • Aspart: 1.4 • Regular: 2.1 • Relative risk: 0.72 (95% CI 0.36 to 1.46), p = NS Minor hypoglycemic events per patient year • Aspart: 86.4 • Regular: 94.5, p = NS • Relative risk: 0.97 (95% CI 0.66 to 1.43), p = NS Maternal outcomes: No significant difference among groups for live births, fetal losses, and congenital malformations	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05 .

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 3. Clinical Trials Evaluating the Rapid-Acting Insulins in Pregnancy (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Persson et al, 2002 ⁶⁵ Experimental parallel: randomized, open-label, multicenter	33	Type 1 diabetes Pregnant, diabetes diagnosis ≥ 2 years, age > 20 years, multi-dose insulin therapy, A1C $< 9\%$	Insulin lispro immediately before meals (n = 16) Regular insulin 30 minutes before meals (n = 17) All patients also received NPH insulin at bedtime and, if needed, before breakfast Duration: 15 weeks gestation to delivery (patients were treated with regular plus NPH before randomization at 15 weeks)	Lispro \geq Regular Post-breakfast glucose (combined results of weeks 21, 28, and 34) • Lispro: 117 ± 57 mg/dL • Regular: 154 ± 67 mg/dL, $p < 0.01$ Post-lunch glucose (combined results of weeks 21, 28, and 34) • Lispro: 121 ± 51 mg/dL • Regular: 122 ± 58 mg/dL, $p = \text{NS}$ Post-dinner glucose (combined results of weeks 21, 28, and 34) • Lispro: 118 ± 50 mg/dL • Regular: 124 ± 49 mg/dL, $p = \text{NS}$	No discontinuation due to adverse events reported Proportion of patients who experienced hypoglycemia • Lispro: 5.5% • Regular: 3.9%, $p < 0.05$ Neonatal outcomes: No significant difference among groups for gestational age at delivery, birth weight, or neonatal complications	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05 .

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 4. Clinical Trials Evaluating the Rapid-Acting Insulins in Children

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Weinzimer et al, 2008 ⁷⁴ Experimental parallel: randomized, open-label, multicenter	296	Type 1 diabetes Children and adolescents 4 – 18 years of age, > 1 year since diagnosis, and A1C ≤ 10% (mean aspart 8 ± 0.94%; mean 8.2 ± 0.84%). All patients had been treated for > 3 months with continuous subcutaneous insulin aspart or lispro.	Insulin aspart by subcutaneous continuous infusion before meals (n = 197) Insulin lispro by subcutaneous continuous infusion before meals (n = 99) Duration: 16 weeks	Aspart = Lispro A1C at 16 weeks <ul style="list-style-type: none"> • Aspart: 7.9 ± 0.93% • Lispro: 8.1 ± 0.85% • Treatment difference met noninferiority criteria Change in A1C at 16 weeks <ul style="list-style-type: none"> • Aspart: -0.15% • Lispro: -0.05%, p = NS 	Discontinuation due to adverse events <ul style="list-style-type: none"> • Aspart: 0% • Lispro: 1/100 (1%) Major hypoglycemic events per patient year (at 16 weeks) <ul style="list-style-type: none"> • Aspart: 0.4 • Lispro: 0.3, p=NS Minor hypoglycemic events per patient year (at 16 weeks) <ul style="list-style-type: none"> • Aspart: 77.2 • Lispro: 66, p=NS Major nocturnal hypoglycemic events per patient year (at 16 weeks) <ul style="list-style-type: none"> • Aspart: 0.1 • Lispro: 0, p=NS 	1
Cherubini et al, 2006 ⁷³ Experimental parallel: randomized, open-label	30	Type 1 diabetes Children (mean age 8.1 years) with mean diabetes duration of 5.2 years, mean A1C of 7.5% in both groups	Insulin aspart 2 minutes before meals and snacks (n = 31) Regular insulin 30 minutes before meals (n = 32) All patients received glargine insulin at bedtime Duration: 12 weeks	Aspart ≥ Lispro Change in A1C at 12 weeks (calculated) <ul style="list-style-type: none"> • Aspart: -0.5%, p = 0.018 vs. baseline • Regular: -0.1%, p = NS vs. baseline 	Hypoglycemic episodes with blood glucose values < 70 mg/dL per patient day <ul style="list-style-type: none"> • Aspart: 0.21 • Regular: 0.18, p = NS Hypoglycemic episodes with blood glucose values < 50 mg/dL per patient day <ul style="list-style-type: none"> • Aspart: 0.045 • Regular: 0.035, p = NS 	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 4. Clinical Trials Evaluating the Rapid-Acting Insulins in Children (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Holcombe et al, 2002 ⁷² Experimental crossover: randomized, open-label, multicenter	463	Type 1 diabetes Patients 9-18 years of age, treated with insulin for ≥ 1 year, no A1C criteria specified (mean A1C lispro 8.4%; mean A1C regular 8.8%)	Insulin lispro immediately before meals Regular insulin 30 – 45 minutes before meals All patients received NPH insulin 1 to 3 times daily for basal coverage. Duration: Patients treated for 4 months and immediately crossed-over to other treatment arm for an additional 4 months	Lispro = Regular Mean A1C at endpoint • Lispro: $8.7 \pm 1.4\%$ • Regular: $8.7 \pm 1.6\%$, p = NS Change in A1C at endpoint (calculated) • Lispro: $+0.3\%$ • Regular: -0.1% (no statistical comparison available)	No patients discontinued treatment due to adverse related to study medications Hypoglycemic events per patient month • Lispro: 4 ± 4.5 • Regular: 4.4 ± 4.5 , p < 0.05 Nocturnal hypoglycemic events per patient month • Lispro: 1 ± 1.9 • Regular: 1.7 ± 2.6 , p < 0.001	1
Deeb et al, 2001 ⁶⁹ Experimental crossover: randomized, open-label, multicenter	61	Type 1 diabetes Children 3 – 12 years of age, ≥ 1 year since diagnosis, treated with insulin for ≥ 2 months, no A1C criteria specified (mean baseline A1C 8.4%)	Insulin lispro within 15 minutes before meals Insulin lispro given immediately after meals Regular insulin 30 – 45 minutes before meals Patients also received basal insulin (NPH, Lente, or Ultralente) per pretrial regimen. Duration: Patients treated for 3 months and immediately crossed-over to other treatment arm for an additional 3 months	Lispro before meals = Lispro after meals = Regular Mean A1C at endpoint • Lispro before meals: 8.4% • Lispro after meals: 8.4% • Regular before meals: 8.5% • p = NS for all inter-treatment comparisons Change in A1C at endpoint (calculated) • Lispro before meals: 0% • Lispro after meals: 0% • Regular before meals: $+0.1\%$ (no statistical comparison available)	No patients discontinued treatment due to adverse related to study medications Hypoglycemic events per patient month • Lispro before meals: 14.7 ± 11.9 • Lispro after meals: 13.6 ± 9.3 • Regular before meals: 13.8 ± 9.8 • p = NS for all inter-treatment comparisons	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 4. Clinical Trials Evaluating the Rapid-Acting Insulins in Children (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Tubiana-Rufi, 2004 ⁷⁵ Experimental crossover: randomized, open-label, multicenter	27	Type 1 diabetes Children < 10 years, using regular insulin via continuous subcutaneous infusion for ≥ 3 months prior to trial, no A1C criteria specified (baseline A1C 8.02%)	All insulins administered as continuous subcutaneous infusions with mealtime boluses <ul style="list-style-type: none"> Insulin lispro 0 – 5 minutes before meals Regular insulin 20 – 30 minutes before meals Duration: Patients treated for 16 weeks and immediately crossed-over to other treatment arm for an additional 16 weeks	Lispro = Regular Change in A1C after initial 16-week period <ul style="list-style-type: none"> Lispro: $+0.15 \pm 0.13\%$ Regular: $+0.11 \pm 0.63\%$, p = NS A1C for second 16-week period not reported due to carryover effects	Discontinuations due to adverse events: 2 patients during second period while on lispro Severe hypoglycemic events per patient month <ul style="list-style-type: none"> Lispro: 11 ± 6.4 Regular: 13.8 ± 8.5, p = NS 	1
Tupola et al, 2001 ⁷¹ Experimental crossover: randomized, open-label, multicenter	24	Type 1 diabetes Children <10 years of age, ≥ 1 year since diagnosis, no A1C criteria specified (mean baseline 8.1)	Insulin lispro immediately before meals Regular insulin 20-30 min before meals All patients received NPH insulin twice daily for basal coverage. Duration: Patients treated for 3 months and immediately crossed-over to other treatment arm for an additional 3 months	Lispro = Regular Change in A1C at endpoint <ul style="list-style-type: none"> Lispro: $+0.2 \pm 0.8\%$ Regular: $-0.4 \pm 0.7\%$, p = NS 	No patients discontinued treatment due to adverse events Hypoglycemic events per patient month <ul style="list-style-type: none"> Lispro: 4.9 Regular: 4.4, p = NS Hypoglycemic events per patient month <ul style="list-style-type: none"> Lispro: 34 Regular: 41, p = NS 	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 4. Clinical Trials Evaluating the Rapid-Acting Insulins in Children (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Ford-Adams et al, 2003 ⁷⁰ Experimental crossover: randomized, open-label, multicenter	23	Type 1 diabetes Children 7-11 years of age, ≥ 1 year since diagnosis, A1C $\leq 12\%$ (mean baseline 8.4%)	Insulin lispro immediately before meals Regular insulin 20-30 min before meals All patients received NPH insulin prebreakfast and before bedtime Patients treated for 4 months and immediately crossed-over to other treatment arm for an additional 4 months	Lispro = Regular A1C at end of initial 4-month period • Lispro: $8.9 \pm 0.3\%$ • Regular: $8.4 \pm 0.3\%$, p = NS A1C at end of second 4-month period • Lispro: $8.5 \pm 0.2\%$ • Regular: $8.8 \pm 0.3\%$, p = NS Change in A1C at end of initial 4-month period (calculated) • Lispro: +0.5% • Regular: 0% (no statistical comparison available) Change in A1C at end of second 4-month period (calculated) • Lispro: +0.1% • Regular: +0.4% (no statistical comparison available)	Hypoglycemic events per patient month • Aspart: 6.4 • Lispro: 6.8, p = NS	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 5. Clinical Trials Evaluating the Rapid-Acting Insulins as Continuous Subcutaneous Infusions

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Bode et al, 2002 ⁷⁶ Experimental parallel: randomized, open-label, multicenter	146	Type 1 diabetes Patients 18 – 71 years of age, \geq 12 months since diagnosis, \geq 3 months treatment with continuous subcutaneous infusions, and baseline A1C of 5.7-9.7% (mean baseline aspart 7.3%; lispro 7.3%; regular 7.5%)	All insulins administered as continuous subcutaneous infusions with mealtime boluses <ul style="list-style-type: none"> • Insulin aspart immediately before meals (n = 59) • Insulin lispro immediately before meals (n = 28) • Buffered regular insulin 30 minutes before meals (n = 59) Duration: 16 weeks	Aspart = Lispro = Regular Change in A1C at 16 weeks <ul style="list-style-type: none"> • Aspart: $0 \pm 0.51\%$ • Lispro: $+0.15 \pm 0.63\%$ • Regular: $+0.18 \pm 0.84$ • p = NS between groups 	Discontinuation due to adverse events <ul style="list-style-type: none"> • Aspart: 1/59 (1.7%) • Lispro: 0% • Regular 0% Hypoglycemic events per patient month <ul style="list-style-type: none"> • Aspart: 6.7 ± 5.4, p < 0.05 vs. lispro and regular • Lispro: 10.5 ± 8.1, p = NS vs regular • Regular: 10.5 ± 8.9 Nocturnal hypoglycemic events per patient month (at 16 weeks) <ul style="list-style-type: none"> • Aspart: 0.5 ± 0.83, p < 0.01 vs. regular; p = NS vs lispro • Lispro: 0.6 ± 0.61, p = NS vs. regular • Regular: 0.9 ± 0.97 	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 5. Clinical Trials Evaluating the Rapid-Acting Insulins as Continuous Subcutaneous Infusions (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Hoogma et al, 2006 ⁷⁷ Experimental parallel: randomized, open-label, multicenter	59	Type 1 diabetes Patients > 18 years of age, > 6 months of continuous subcutaneous insulin infusion, A1C \leq 8.5% (mean baseline: 6.9%)	All insulins administered as continuous subcutaneous infusions with mealtime boluses <ul style="list-style-type: none"> Insulin aspart immediately before meals (n = 30) Insulin glulisine immediately before meals (n = 29) Duration: 12 weeks	Aspart = Glulisine Change in A1C at 12 weeks <ul style="list-style-type: none"> Aspart: +0.1% Glulisine: +0.2% Treatment difference between groups: 0.11 (95% CI: -0.09 to 0.31) 	Patients experiencing \geq 1 hypoglycemic event <ul style="list-style-type: none"> Aspart: 24/30 (80%) Glulisine: 26/29 (89.7%), p value not reported 	1
Renner et al, 1999 ⁸¹ Experimental crossover: randomized, open-label, multicenter	113	Type 1 diabetes Patients (mean age 37.1 years) \geq 2 years since diagnosis, \geq 6 months treatment with continuous subcutaneous insulin infusion prior to trial, A1C not specified (mean baseline 7.24%)	All insulins administered as continuous subcutaneous infusions with mealtime boluses <ul style="list-style-type: none"> Insulin lispro Regular insulin Duration: Patients treated for 4 months and immediately crossed-over to other treatment arm for an additional 4 months	Lispro > Regular Mean A1C at treatment endpoints <ul style="list-style-type: none"> Lispro: $6.77 \pm 0.88\%$ Regular: $6.9 \pm 0.97\%$, p = 0.02 vs. lispro Change in A1C at endpoint (calculated) <ul style="list-style-type: none"> Lispro: -0.47% Regular: -0.34% (no statistical comparison available) 	Discontinuation due to adverse events not reported Hypoglycemic episodes per patient month <ul style="list-style-type: none"> Lispro: 13.6 ± 7.8 Regular: 13.6 ± 7.5, p = NS 	1
Raskin et al, 2001 ⁸⁰ Experimental crossover: randomized, open-label, multicenter	58	Type 1 diabetes Patients 13 to 60 years of age, \geq 6 months treatment with continuous subcutaneous insulin infusion prior to trial, A1C < 2 times the upper limit of normal range	All insulins administered as continuous subcutaneous infusions with mealtime boluses <ul style="list-style-type: none"> Insulin lispro before meals Regular insulin before meals Duration: Patients treated for 3 months and immediately crossed-over to other treatment arm for an additional 3 months	Lispro > Regular Mean A1C at endpoint <ul style="list-style-type: none"> Lispro: $7.41 \pm 0.97\%$ Regular: $7.65 \pm 0.85\%$, p = 0.004 Change in A1C at endpoint <ul style="list-style-type: none"> Lispro: $-0.34 \pm 0.59\%$ Regular: $-0.09 \pm 0.63\%$, p = 0.004 	One patient withdrew from study early for personal reasons. Treatment group at time of withdrawal was not reported. Patients experiencing \geq 1 hypoglycemic event <ul style="list-style-type: none"> Lispro: 7 patients Regular: 7 patients 	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 5. Clinical Trials Evaluating the Rapid-Acting Insulins as Continuous Subcutaneous Infusions (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Johansson et al, 2000 ⁷⁸ Experimental crossover: randomized, open-label, single-center	41	Type 1 diabetes Patients 20 to 58 years of age, ≥ 6 months treatment with continuous subcutaneous insulin infusion prior to trial, A1C $< 9\%$ (mean baseline 7.7%)	All insulins administered as continuous subcutaneous infusions with mealtime boluses <ul style="list-style-type: none"> Insulin lispro 5 minutes before meals Regular insulin 30 minutes before meals Duration: Patients treated for 2 months and immediately crossed-over to other treatment arm for an additional 2 months	Lispro > Regular Mean A1C at treatment endpoint <ul style="list-style-type: none"> Lispro: 7.4% Regular: 7.6% Treatment difference: -0.2% (95% CI 0 to 0.3%) $p = 0.047$ Change in A1C at endpoint (calculated) <ul style="list-style-type: none"> Lispro: -0.3% Regular: -0.1% (no statistical comparison available)	No discontinuations due to adverse events Hypoglycemic episodes per patient month <ul style="list-style-type: none"> Lispro: 9.7 Regular: 8, $p = \text{NS}$ 	1
Melki et al, 1998 ⁷⁹ Experimental crossover: randomized, open-label, multicenter	39	Type 1 diabetes Patients 18 – 60 years of age, ≥ 12 months treatment with continuous subcutaneous insulin infusion prior to trial, A1C $< 8.5\%$ (mean baseline lispro 7.7%; regular 8%)	All insulins administered as continuous subcutaneous infusions with mealtime boluses <ul style="list-style-type: none"> Insulin lispro immediately before meals Regular insulin 20 – 30 minutes before meals Duration: Patients treated for 3 months and immediately crossed-over to other treatment arm for an additional 3 months	Lispro > Regular Mean A1C at end of initial 3-month period <ul style="list-style-type: none"> Lispro: $7.11 \pm 0.15\%$ Regular: $7.88 \pm 0.16\%$, p value not reported Change in A1C at end of initial 3-month period <ul style="list-style-type: none"> Lispro: $-0.62 \pm 0.13\%$ Regular: $-0.09 \pm 0.15\%$, $p = 0.01$ A1C for second 3-month period not reported due to carryover effects	One patient withdrew from study early due to noncompliance with protocol. Treatment group at time of withdrawal was not reported. Hypoglycemic episodes per patient month (data from first 3-month period only) <ul style="list-style-type: none"> Lispro: 7 ± 0.9 Regular: 7.9 ± 0.9, $p = \text{NS}$ 	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05 .

* Grade of Evidence. Refer to Appendix A for definitions.

Evidence Table 5. Clinical Trials Evaluating the Rapid-Acting Insulins as Continuous Subcutaneous Infusions (continued)

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes		Grade*
				Clinical Results	Discontinuation & Adverse Events	
Zinman et al, 1997 ⁸² Experimental crossover: randomized, double-blind	30	Type 1 diabetes Adult patients (range 26 – 51 years of age), >3 months treatment with continuous subcutaneous insulin infusion prior to trial, no A1C criteria specified (mean baseline 8.03%)	All insulins administered as continuous subcutaneous infusions with mealtime boluses <ul style="list-style-type: none"> Insulin lispro 0 – 5 minutes before meals Regular insulin 0 – 5 minutes before meals Duration: Patients treated for 3 months and immediately crossed-over to other treatment arm for an additional 3 months	Lispro > Regular Mean A1C at endpoint <ul style="list-style-type: none"> Lispro: $7.66 \pm 0.13\%$ Regular: $8 \pm 0.16\%$ Treatment difference: -0.34%, $p = 0.004$ Change in A1C at endpoint (calculated) <ul style="list-style-type: none"> Lispro: -0.37% Regular: -0.03% (no statistical comparison available)	Discontinuation due to adverse events not reported Hypoglycemic episodes per patient month <ul style="list-style-type: none"> Lispro: 8.6 ± 1.4 Regular: 10.8 ± 1.8, $p = \text{NS}$ 	1

Abbreviations: A1C = hemoglobin A_{1c}; CI = confidence interval; N or n = number of evaluable patients in trial or treatment group; NPH = neutral protamine hagedorn insulin; NS = not statistically significant, p value > 0.05.

* Grade of Evidence. Refer to Appendix A for definitions.